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A QUANTITATIVE TEST OF THEORY AND DIAGNOSTIC INDICATORS OF CHILDHOOD SCHIZOPHRENIA

LAURETTA BENDER, M.D.
AND
WILLIAM H. HELME, M.A.
NEW YORK

PURPOSE OF THE STUDY

THE PRESENT study is a first step toward establishing objective tests of criteria by which childhood schizophrenia can be differentiated from other serious behavior disorders of children. Many approaches to the problems of differential diagnosis may be taken. These approaches do not differ in the objectivity of the observations recorded, for this is an ideal toward which all scientific workers strive. Rather, they differ as to what aspects of behavior are observed and how the results of observations are organized.

The aspects of behavior recorded in this investigation were chosen on the basis not only of clinical experience but also of their offering a test of working hypotheses derived from a systematic theory of childhood schizophrenia. Over a span of nearly two decades (1934-1952) about 7,000 children referred to the children's service of the Psychiatric Division of Bellevue Hospital were examined, tested, observed, cared for, and referred to homes and institutions for more permanent care and therapeutic aid. Those who worked with these children came from a variety of theoretical backgrounds: psychoanalytic, neuropsychiatric, behaviorist, gestalt. Their concern for the care of the actual child in the immediate situation was perhaps the one factor they held in common. Out of this diversity of views, under the leadership of Paul Schilder and Lauretta Bender, an increasingly articulated theoretical view has gradually emerged. As with all theories in constant contact with practice, new experiences and observations have modified it continually. The core of the theory, however, has continued to grow and to become more integrated as the changes progressed. With the improvement of diagnostic measures and observational techniques, it appeared feasible to formulate the theory in such a way as to permit objective tests of its working hypotheses. This report describes the results obtained in the first step toward verification, and the consequent rejection and reformulation of specific aspects of the theory. The case records used were obtained from an early

From the Psychiatric Division of Bellevue Hospital and the New York University College of Medicine.

This investigation has been supported by a research grant from the National Institute of Mental Health, of the National Institutes of Health, United States Public Health Service.

Alfred M. Freedman, M.D.; Alvin Eldridge Grugett Jr., and W. R. Keeler, M.D., assisted in the skilled and exacting task of evaluating and classifying data from the case records; and Saul Gurevitz, Ph.D., provided independent evaluations of the projective material.

stage of the theoretical development, and the original recordings from which the present tabulations were made were written by professional workers whose own theoretical orientations differed widely.

THEORY

For purposes of this study, the theory has been formulated under six general propositions.[1]

Theoretical Propositions.—I. Childhood schizophrenia is a disorder in the regulation of the maturation of basic behavior processes. Characteristically, it is a disorder of the whole organization of such processes. It is not confined to a single process or to a set of processes involving but one major aspect of behavior. Thus, its effects are to be found in disturbances of many areas of functioning, e. g., homeostatic control, vasovegetative functioning, perceptual organizing of sensory data, motility and postural responses, and coordinated control of voluntary musculature.

II. The neurological hierarchy and control remain primitive, resembling in many aspects the organization of behavior found in the fetal stages of development.

III. Development of particular neuropsychological subsystems, however, is not necessarily arrested at fetal levels. Therefore the behavior largely mediated by such subsystems may reveal normal progress, or even precocity. But the utilization of such processes in the service of the whole developing organism will still be impaired. Particularly in intellectual functions, such as rote memory or creativity in drawings, are examples of such precocious functioning likely to be found.

IV. For purposes of analysis, overt behavior disturbances in childhood schizophrenia may be divided as follows:

A. Primary disturbances of both voluntary and autonomic functions, as mentioned in Proposition I.

B. Anxiety arising from the experience of primary disturbances.

C. Secondary disturbances in the basic perception of the self as an object in the psychological world of the child, arising from the primary ones. Disturbances in body image, identity, and orientation to impersonal objects and forces from the outer world would be included here.

D. Secondary disturbances in the area of social orientation and functioning. Disturbances in the view of the self as a social object, in the perception of other persons, and in the forming and maintaining of social relationships would be noted here.

V. In global terms, three general types of coping with primary disturbances and the resultant anxiety may be distinguished:

A. Secondary neurotic habit patterns may be used. These are evidence of a struggle for ego maturity and health.

1. For earlier and current formulations of the theory elsewhere, the reader is referred to the following articles: Bender, L.: (*a*) Childhood Schizophrenia: A Clinical Study of 100 Schizophrenic Children, Am. J. Orthopsychiat. **17**:40-56, 1947; (*b*) Anxiety in Disturbed Children, in Hoch, P., and Zubin, J., Editors: Anxiety, New York, Grune & Stratton, Inc., 1949. (*c*) Bender, L., and Freedman, A. M.: A Study of the First Three Years in the Maturation of Schizophrenic Children, Quart. J. Child Behavior, to be published.

B. Increased development and precocious patterning in particular areas may be used. Unable to establish a more general stable ego-world relation, the child may select a special region of communication with his world.

C. Surrender to a more or less unpatterned torporous state may take place.

Combinations of these three general ways of coping with his problems and anxiety are, of course, possible for a given child.

VI. To explain the disturbances manifested in the behavior of the schizophrenic child, the term plasticity has been introduced. Plasticity is a "whole" quality of the child's psychological and biological organization. It connotes instability and poorly integrated control and direction of behavior on all levels. Biological rhythms and tempos are disturbed and inconstant. Boundaries between psychological regions tend to shift and be permeated more easily than in the normal child. For example, symbols and the concrete material objects they represent are confused: The same child may appear excessively concrete in his thinking at one point and overabstract at another. Likewise, bizarre or "arbitrary" associations can be considered as manifestations of permeable boundaries between psychological regions. There are four principal ways in which plasticity of organization is expressed in behavior:

A. Percepts and memory traces of objects, which are perceived separately or in clearly defined relationship in the normal person, seem to be distorted by mutual influences in the brain of the schizophrenic child. The result is distortion, confusion, and perseveration in schizophrenic reproductions and drawings.

B. Influence of stimuli impinging on the schizophrenic child's world are unduly intense and disorganizing in their effects. The result is extremes of response or nonresponse, in action and feelings.

C. Influences of other persons constitute the most striking examples of overintense experience and response. The result is that the child is restricted to an impoverished choice of responses: (1) surrender, in which the boundary between self and others is lost; (2) total opposition, in which the child's behavior is entirely taken up with resistance to surrender, or (3) withdrawal, in which virtually no sign of awareness of the other person is permitted.

D. An all-pervasive pananxiety is experienced. It can be considered the counterpart in awareness of the chaotic and unstable organization of the child's psychobiological system as a whole.

Selection of Sample and Items for Study.—The first criterion for choosing the sample for this introductory study was confirmation of diagnosis by follow-up observation. A follow-up study had been conducted from 1950 to 1952, under a grant from the Mental Health Institute of the United States Public Health Service, of patients treated at Bellevue Hospital beween 1934 and 1946.[14] The study confirmed the original diagnosis of childhood schizophrenia in 66 to 87% of cases, depending on the criteria used. From this pool of 120 cases, 30 were chosen in which confirmation of diagnosis by staff members of other institutions was complete. These 30 cases were all from the earlier period, 1934 to 1942, during which pentylentetrazol U. S. P. (Metrazol) shock treatment was administered. Thus, the shortest period of follow-up study was eight years, and the youngest patient at the time of the follow-up interview was already in middle adolescence.

A second criterion for choosing the sample was adequacy of data available in the case records. Since the study was dependent on the extent of observations, tests,

and interview recorded, it was important to minimize the possibility of certain behavior being shown by the child but omitted from the record.

A control group of 30 children was then chosen, approximately matched for age, sex, and socioeconomic status of family (Table 1). This group was composed of children admitted to the ward during the same period as the schizophrenic group, but with a diagnosis of nonpsychotic disease, confirmed by later follow-up observation.

TABLE 1.—*Comparison of Schizophrenic and Control Groups* on Age and Socioeconomic Status*

Age	No. of Children: Schizophrenic	No. of Children: Control
14	1	1
13	2	0
12	8	4
11	4	5
10	6	6
9	2	1
8	4	7
7	1	3
6	1	2
5	1	1
Mean	10.77	9.83
S. D.	2.13	2.14
Critical ratio of difference is 1.68, not significant		

Socioeconomic Status	No. of Children: Schizophrenic	No. of Children: Control
Above average	1	1
Average	11	7
Below average	5	3
Low	13	19
Chi-square, average ranges vs. low range is 1.67 (1 degree of freedom), not significant		

* Comparison was also made of the number of children in foster homes. There were four such children in each group.

TABLE 2.—*Diagnostic Composition of Control Group*

Category	No. of Patients
Primary behavior problem, neurotic traits	11
Primary behavior problem	3
Psychoneurosis, obsessive-compulsive	2
Psychoneurosis, other	4
Psychopathic personality	4
Dull normal; reading disability	1
Mental deficiency	3
Organic brain disorder	2

The next step was to select the items to be tabulated from the case records. Selection was based on (*a*) the positive requirements of the theory; (*b*) the inclusion of observations which, while important in the total behavior pattern of the child, would not be expected to differentiate schizophrenic from other disturbed children, and (*c*) objectivity of evidence in the record for the given item.

The theoretical propositions required that disturbances in the schizophrenic child be distributed over many areas of functioning, as follows:

1. Homeostatic and vasovegetative behavior, including the establishment of patterns of eating, sleeping, and elimination.

2. Neurological functioning, as shown in balance, postural, and voluntary motor control.

3. Perception of and response to physical reality, including body image, reality testing, and perception of physical objects and forces in the child's world.

4. Anxiety and affect, with the attempts to cope with it. Both basic anxiety and anxiety reactive to social experiences would be expected.

5. Perception and response to social stimulation. Here, it would be desirable to differentiate perception of the self as a social object from body image *per se*. Social response would include both interpersonal relationships and relations to social authority and structure.

6. Intellectual functioning on standardized measures of intelligence and scholastic achievement.

Table 3 shows the items tabulated from the case records, with the sources of data on which each tabulation is based. Tabulations were made by two members of a group of four workers, i. e., two psychiatrists, one psychologist, and one social worker. Each "team" included one psychiatrist and one of the other workers. No rating of "pathological" was made on any item unless both members of the team rated it so independently. In addition, all ratings of drawings were checked independently by another psychologist, with particular experience in this area. While it was not possible to conceal the identities of the records in terms of diagnostic classification, several cross checks of records and parts of records indicated that objectivity had been substantially achieved. The major assurance of objectivity consisted, of course, in the operational definitions of specific items. For example, anxiety was never inferred from subtleties of expression; overt evidence, such as habitual crying or spontaneous verbalizing of feeling, was required. Likewise, attitudes toward parents were accepted only when definite acts or clear and consistent verbal or emotional expression was observed; inferences from possible symbols in play or fantasy were used only to corroborate behavioral data. It is likely that in a study in which observations of play were objectively categorized beforehand such caution in regard to symbols, etc., would not be necessary or desirable.

Predictions on specific items, made from the theory, fall into three classes. First, those items which measure aspects of behavior mediated to a very limited extent by social learning should reveal a moderately high incidence of pathological cases in the schizophrenic group and few or no such cases in the control group. Second, those items which measure aspects of behavior found only in certain nonpsychotic disorders, represented in the control group (and in the schizophrenic), should reveal a higher incidence in the schizophrenic group, but a number of cases in the control group is to be expected. Finally, those items which measure aspects of behavior common to all disturbed children should reveal no significant differences. There is a fourth possibility, namely, that some manifestations of pathology requiring a high degree of organization for their use may occur more frequently in the control group, but this category would be difficult to demonstrate. The reason is that if an alternative mode of response is preferred by the schizophrenic group, e. g., withdrawal, there would be a natural reciprocal effect on other modes.

In addition to predictions from theory on single items, there is the possibility of predicting higher incidences of plural symptoms in a given area for a schizophrenic patient than for a control patient. Furthermore, the theory requires that, even if incidences in given areas do not differ significantly between the groups, a given schizophrenic child should tend to show pathology in more areas than does the control child.

TABLE 3.—*Items on Recording Form for Data from Case Records*

Category	Item	Scoring	Source of Data
I A Homeostatic and vaso-vegetative behavior	Height	— 0 +	First physical examination
	Weight	— 0 +	First physical examination
	Response to pain	0 1	Nurses' or psychiatrist's notes
	Response to illness	0 1	Nurses' or psychiatrist's notes
	Response to noise	0 1	Nurses' or psychiatrist's notes
	Vascular abnormality	0 1	Nurses' or psychiatrist's notes
	Homeostatic abnormality	0 1	First physical examination or notes
I B Habit formation and maintenance	Eating regularity	0 1	Nurses' notes; parent interviews
	Eating quantity	— 0 +	Nurses' notes; parent interviews
	Eating dependence	0 1	Nurses' notes; parent interviews
	Sleeping regularity	0 1	Nurses' notes; parent interviews
	Sleeping quantity	— 0 +	Nurses' notes; parent interviews
	Sleeping dependence	0 1	Nurses' notes; parent interviews
	Elimination learning	— 0 +	Parent interviews
	Elimination regularity	0 1	Parent interviews; nurses' notes
IIA	Amount of motor activity	— 0 +	Nurses' or psychiatrist's notes; outside reports
Neurological functioning	Whirling	0 1	Neurological, psychiatric examination
	Support (cohesiveness)	0 1	Neurological, psychiatric examination
	Tonus	0 1	Neurological, psychiatric examination
	Catalepsy; catatonia	0 1	Neurological, psychiatric examination
	Adduction-abduction	— 0 +	Neurological, psychiatric examination
	Fine coordination	0 1	Neurological, psychiatric examination nurses' notes
	Gross coordination	0 1	Neurological, psychiatric examination; nurses' notes
	Gait	0 1	Neurological, psychiatric examination; nurses' notes
	Tics	0 1	Neurological, psychiatric examination; nurses' notes
	Grimacing	0 1	Psychiatric examination; ward observation
	Primitive reflexes	0 1	Neurological examination
	Deep reflexes	— 0 +	Neurological examination
	Ocular movements	0 1	Neurological examination
	Ocular convergence	0 1	Neurological examination
IIB Acquired motor skills	Learning to walk	— 0 +	Parent interviews
	Learning to talk	— 0 +	Parent interviews
	Voice pitch, control	0 1	Ward observation
	Speech coordination and use	0 1	Ward observation
IIC	Perceptual-motor organization	.....	Bender gestalt test; insufficient data obtained on control group
IIIA Body image	Integration	0 1	Goodenough drawing of man
	Posture; balance	0 1	Goodenough drawing of man
	Proportions		
	Head	— 0 +	Goodenough drawing of man
	Trunk	— 0 +	Goodenough drawing of man
	Arms	— 0 +	Goodenough drawing of man
	Legs	— 0 +	Goodenough drawing of man
IIIB Self-world perceptions	Integration	0 1	Free drawings
	Rigidity-plasticity	— 0 +	Free drawings; Goodenough test
	Movement pathology	— 0 +	Free drawings; Goodenough test
	Suspension pathology	— 0 +	Free drawings
	Outlining	— 0 +	Free drawings
	Use of color	— 0 +	Free drawings
	Detail	— 0 +	Free drawings
	Fittingness of content	0 1	Free drawings
	Overabstraction	0 1	Free drawings
	Pathognomonic content	0 1	Free drawings
IIIC Reality testing and fantasy	Productivity of fantasy	— 0 +	Drawings, dreams; play
	Symbolic-concrete differentiation	0 1	Dreams; play; psychometric verbalization
	Reality-fantasy differentiation	0 1	Psychiatric interviews
	Hallucinations		Psychiatric interviews; observations
	Visual	0 1	
	Auditory	0 1	
	Other	0 1	
	Identity confusion	0 1	Psychiatric interviews; observations
	Introjected bodies; somatic delusions	0 1	Psychiatric interviews; nurses' notes
	Orientation confusion	0 1	Psychiatric interviews; nurses' notes
	Space-time-movement concern	0 1	Psychiatric interviews; play; nurses' notes
	Rigidity-plasticity	0 1	Verbalized fantasies; play
IVA Manifest anxiety	Diffuse anxiety	0 1	Psychiatric and nurses' notes
	Self-anxiety	0 1	Psychiatric and nurses' notes
	Anxious response to fantasy	0 1	Psychiatric and nurses' notes
	Anxiety over sex	0 1	Psychiatric and nurses' notes
IVB Neurotic mechanisms; affect	Compulsions	0 1	Psychiatric and nurses' notes
	Depression	0 1	Psychiatric and nurses' notes
	Emotional expression, inappropriate	0 1	Psychiatric and nurses' notes
	Fatigue	0 1	Psychiatric and nurses' notes
	Hypochondria	0 1	Psychiatric and nurses' notes
	Lethargy, irritability	— 0 +	Psychiatric and nurses' notes
	Obsessions	0 1	Psychiatric and nurses' notes
	Phobias	0 1	Psychiatric and nurses' notes

TABLE 3.—*Items on Recording Form for Data from Case Records—Continued*

Category	Item	Scoring	Source of Data
IVC Neurotic acts	Fire setting	0 1	Parent interviews; referral data
	Destruction of objects	0 1	Observations on ward; play; parent interview
	Stealing	0 1	Parent interviews; referral data
VA Self-concept	Self-hostility	0 1	Psychiatric interviews; nurses' notes
	Self-deprecation	0 1	Psychiatric interviews; nurses' notes
	Self-destruction	0 1	acts Psychiatric interviews; fantasy; reported
VB Sex expression	Identity confusion	0 1	Psychiatric interviews
	Identity with female role	0 1	Psychiatric interviews
	Masturbation	0 1	Parent interviews; psychiatric notes; referral data
	Obscenity	0 1	Parent interviews; psychiatric notes; referral data
	Self-exposure	0 1	Parent interviews; psychiatric notes; referral data
	Voyeurism	0 1	Parent interviews; psychiatric notes; referral data
	Homosexual activity, with peer	0 1	Parent interviews; nurses' notes; referral data
	Homosexual activity, with adult	0 1	Parent interviews; referral data
	Heterosexual activity	0 1	Parent interviews; referral data
VC Perception of other persons and response	Father, rejection experience	0 1	Referral data; fantasy; play; psychiatric and parent interviews *
	Father, fear experience	0 1	
	Hostility-affection to father	− 0 +	
	Dependence-independence to father	− 0 +	
	Withdrawal from father	0 1	
	Same items, mother		
	Same items, sibling		
	Same items, peers		
	Same items, hospital adult		
	Same items, outside adult		
VD Response to authority	Withdrawal		
	Ward	0 1	
	Home	0 1	
	School	0 1	
	Hostility		
	Ward	0 1	
	Home	0 1	
	School	0 1	
	Passive resistance		
	Ward	0 1	
	Home	0 1	
	School	0 1	
	Compliance		
	Ward	0 1	
	Home	0 1	
	School	0 1	
	Manipulation		
	Ward	0 1	
	Home	0 1	
	School	0 1	
VI Intellectual functioning	I. Q., objective	Quantitative score	Psychometric tests: Stanford-Binet; Wechsler-Bellevue; Arthur Point Scale; Goodenough test; standard achievement tests
	I. Q., expressive	Goodenough scale	
	Verbal minus performance	− 0 +	
	Reading	Grade equivalent	
	Arithmetic	Grade equivalent	

* The sources of data for each item of categories VC and VD were similar and have not been repeated in the table.

Finally, particularly in the social areas, it is likely that incidences of pathology will be high for both groups, but differences may be expected in such relations as consistency between the expressed social perception and the demonstrated social response. Such differences would be expected, in addition to differences in the incidence of particular modes of response. We shall turn now to a tabulation of the findings on specific items in relation to the working hypotheses.

RESULTS AND COMMENT

Tables 4 to 8 present the tabulations for items or groups of related items. Groupings were made in those instances in which the incidence of a particular manifestation of pathology was too small to be handled statistically. Detailed tabulations for every single item are not given here, since the size of the sample does not warrant it.

Tables 4 to 8 show the incidence of the behavior or observation covered for each item in the schizophrenic and in the control group. The chi-square of the difference and the level of significance are shown. In addition, the prediction of difference according to the theory is noted, categorized as (A) significant incidence expected for the schizophrenic group, virtually zero incidence for the control group; (B) incidence for both groups, but significantly higher for the schizophrenic group, or (C) relatively high incidence for both groups, but with no significant difference.

In general, differences of the A category are predicted for observations of physiological or psychological processes not mediated to any appreciable extent by socializing forces. Differences of the B category are predicted for observations of physiological or psychological behavior affected by socializing forces, but in which the characteristic disorganization of the schizophrenic child leads to more serious disturbance than does the special, relatively localized disturbance of the "behavior-problem" or the psychoneurotic child. That is, the neurotic child is likely to have a number of critical areas in which his problems are focused. In such an area a simple recording of "pathology present" will include certain members of the control group, but it will include more members of the schizophrenic group because the basic disturbance in organization extends to many more areas. Thus, a statistical comparison will reflect the higher probability that the pandisturbance of the schizophrenic brings to any specific area. Differences of the C category are predicted for observations of pathology common to most disturbed children, particularly in social relations, and the neurotic symptoms which arise when the child is unable to cope with social situations in a productive way. Thus, similar incidences may be expected, even though the basic cause of the schizophrenic child's failure to cope with the situation is quite different from the cause of the neurotic child's failure. These general points are applied specifically to the data in Tables 4 to 8.

Vasovegetative and Motor Areas.—First, in the vasovegetative and homeostatic areas of functioning, the prediction is B for height-weight aberrations because external factors, such as malnutrition from neglect, and internal factors, such as neurotic disturbance, can both affect height-weight deviation. The postulation of a more fundamental disturbance in schizophrenia, however, leads to the prediction of a higher incidence there. The observed trend is in the predicted direction. Since it is not significant at the 0.10 level, however, it is listed as B in the observation column, signifying that direction is confirmed but that more cases are needed to reject the null hypothesis. It is interesting to note that disparity between height and weight in the individual does show a difference significant at the 0.10 level, however. This point is being checked more precisely on patients recently admitted to the children's service by Dr. Alfred Freedman, using the Wetzel Grid method.

The prediction for disturbances in response to pain, illness, and noise and for vascular and homeostatic abnormalities must be A, since there is little reason to expect their occurrence in the nonpsychotic patient. The results fully support the hypothesis.

The prediction for disturbances in eating and sleeping habits is clearly in the B category; but when only disturbance in establishing and maintaining a regular pattern for eating and sleeping is considered, the prediction is A. These trends are confirmed, although it seems safer to characterize the observed 11 : 3 ratio on patterning as B rather than A. In elimination habits, however, the typical problems

that arise in toilet training for children in general suggest that any disturbance is likely to affect these habits adversely. The prediction of C is confirmed.

In the motor area overactivity is to be expected in most disturbed children. However, marked underactivity, being expected, as a rule, only in children with organic or glandular disorders, should appear rarely in the control group. The hypothesis is confirmed. Of the eight children showing underactivity, four had periods of overactivity as well—a variation in behavior not observed in the control group.

An important confirmation of the theory of schizophrenia is found in regard to postural and balancing responses. When all abnormalities are combined, the prediction is B. But when only the tonic neck reflex responses of whirling and cohesiveness are included, the prediction of A receives substantial confirmation. The regressive reflexes (Babinski sign in these cases) appear only in the schizophrenic group, as

TABLE 4.—*Predictions and Results for Vasovegetative and Motor Areas*

Item	Incidence: Schizophrenic	Incidence: Control	Chi-Square	*P*	Prediction	Observation
Some abnormality in height-weight	14	7	2.63	....	B	(B)
Height-weight disparateness, one abnormal	8	2	3.00	0.10	B	B
Vascular or homeostatic abnormality	13	0	14.14	0.001	A	A
Some abnormality in eating habits	10	3	3.54	0.10	B	B
Some abnormality in sleeping habits	9	5	0.83	....	B	(B)
Some abnormality in elimination habits	7	5	0.10	....	C	C
Irregular eating-sleeping patterns	11	3	4.56	0.04	A	B
Enuresis	6	11	1.31	....	C	C
Motor hyperactivity	13	15	1.74	....	C	C
Motor hypoactivity and hyperactivity	8	0	5.88	0.02	A	A
Abnormalities of posture, balance	22	7	13.07	0.001	B	B
Whirling and/or cohesiveness	20	3	25.48	0.001	A	A
Some abnormality in coordination	14	11	0.27	....	B	C
Abnormal gross coordination, gait	12	5	2.92	0.10	B	B
Grimacing	6	6	0.00	....	C	C
Tics	7	3	1.08	....	C	(B)
Regressive reflexes	2	0	....	....	A	(A)
Deep reflex abnormality	6	4	0.12	....	B	C
Walking-talking learning, early or late	11	11	0.00	....	B	C
Voice or speech abnormality	22	8	11.33	0.001	B	B

predicted, but the observed incidence is too small for statistical significance. The hypothesis is not confirmed in regard to deep reflex abnormalities or abnormalities in coordination. When the latter are restricted to gross coordination, particularly gait, the prediction is upheld, however.

The hypothesis that voice-speech functions, requiring a high degree of organization, would be oftener disturbed in the schizophrenic group is confirmed. But the expectation of precocious or late learning to walk or talk is refuted by the data. It seems fair to mention, however, that the only source of such data, parental reminiscence, may be open to some question.

In summary, for the vasovegetative and motor areas the predictions from theory fare as follows:

	Observed				
Predicted	A	(A)	B	(B)	C
A	3	1	1	0	0
B	0	0	5	2	3
C	0	0	0	1	4

Full confirmation is 60%; possible confirmation is 25% more.

Body Image, Self-World Perceptions, and Reality Testing.—In the areas of body image and self-world perceptions striking results are found. The aspects of body-image integration, balance, and proportions, if reflected in relatively pure form in the figure drawings, should be predicted as A. But the evidence from other studies of the test strongly suggest that the drawings reflect body image and the social self-concept in combination. We should expect more serious disturbance in the schizophrenic group, however; thus, the prediction is B. It is not confirmed. It is likely that the fault lies neither in the theory nor the test, however, since it has been demonstrated as a powerful diagnostic tool in differentiating schizophrenia from other childhood disorders. It seems clear that better articulation of the aspects to be rated must be made.

TABLE 5.—*Predictions and Results for Body Image, Self-World Perceptions, and Reality Testing*

Item	Incidence		Chi-Square	*P*	Prediction	Observation
	Schizophrenic	Control				
Body-image integration	5	7	0.07	....	B	C
Posture; balance	15	13	0.07	....	B	C
Some abnormal proportions in image	18	19	0.00	....	B	C
Poor integration in self-world perception	14	7	2.63	....	B	B
Rigidity	4	10	2.33	....	C	C
Plasticity	26	16	6.43	0.02	B	B
Rigid-plastic variation	17	7	5.62	0.02	A	B
Movement pathology	20	6	11.47	0.001	A	B
Suspension pathology	21	13	3.32	0.10	A	B
Outlining pathology	23	9	11.31	0.001	B	B
Heavy outlining only	16	2	13.41	0.001	A	A
Color use abnormal	15	3	9.60	0.01	A	A
Detailing abnormal	20	7	9.69	0.01	B	B
Fittingness of content abnormal	11	3	4.56	0.04	B	B
Overabstraction	9	2	4.01	0.05	A	A
Pathognomonic content	15	11	0.61	....	C	C
Fantasy overproductivity	18	9	4.30	0.05	B	B
Fantasy underproductivity	8	7	0.00	....	C	C
Symbol, reality, projective abnormality	16	6	5.81	0.02	B	B
Hallucinations	13	4	5.26	0.03	B	B
Reality confusion	10	2	5.11	0.03	A	A
Identity confusion	11	0	11.15	0.001	A	A
Somatic delusions; introjected bodies	7	1	3.00	0.10	A	A
Orientation confusion	15	1	14.48	0.001	A	A
Space-time-movement concern	11	2	6.29	0.02	A	A
Rigidity; plasticity	9	2	4.00	0.05	A	A

In contrast, all predictions on the free drawings receive confirmation except the one of integration. There was evidence from the judges' disagreement on ratings that this aspect was, like the aspects of the figure drawing, poorly defined. The predictions on the free drawings emphasize the hypothesis that pathognomy in regard to movement, suspension, heavy outlining (boundary emphasis), color, and abstraction are primarily schizophrenic characteristics. Some of these show appreciable incidence in the control group, but always the pathognomy is significantly more frequent in the schizophrenic group. The theoretical significance of confirmations in the free drawings seems to be in characterizing the schizophrenic disturbance as a basic organizational and structural one, rather than a disturbance of content alone. It is noteworthy, also, that over-all rigid control appears more frequently in

the nonpsychotic group—10:4—but the rudimentary control of heavy outlining, reflecting the problem of boundary maintenance in the psychological world, is almost exclusively a property of the schizophrenic group—16:2.

In the area of reality testing predictions are substantially confirmed. Of most theoretical interest here is the fact that identity and orientation confusion so clearly characterizes the schizophrenic group. Projective aberrations, on the other hand, appear in the control group as well, though with less frequency. Possibly reality testing is too global a concept to be used in precise differentiation among seriously disturbed children. It may be fruitful to try to see just what anchors or foundations in reality remain and which ones are swept away, in hallucinations, for example.

In summary, predictions in regard to body image, self-world perceptions, and reality testing fare as follows:

	Observed				
Predicted	A	(A)	B	(B)	C
A	8	1	3	0	0
B	0	0	8	0	3
C	0	0	0	0	3

Full confirmation is 73%; partial or possible confirmation is 15%.

TABLE 6.—*Predictions and Results for Anxiety and Neurotic Symptoms and Acts*

Item	Incidence		Chi-Square	*P*	Prediction	Observation
	Schizophrenic	Control				
Diffuse anxiety	23	11	8.26	0.01	B	B
Anxiety about self	20	18	0.07	....	C	C
Anxious response to fantasy	8	6	0.09	....	C	C
Anxiety about sex	10	8	0.11	....	C	C
Compulsions	13	11	0.14	....	C	C
Depression	2	5	....	....	C	C
Inappropriate emotional expression	7	4	0.44	....	B	C
Fatigue	5	3	....	....	B	C
Hypochondria	5	2	....	....	C	C
Lethargy	8	5	0.19	....	B	C
Irritability	18	10	3.28	....	B	B
Obsessions	7	6	0.00	....	C	C
Phobias	8	4	0.94	....	C	C
Neurasthenic responses (fatigue, lethargy, irritability)	23	14	4.51	....	B	B
Neurotic fears (hypochondria, phobias)	13	6	2.77	....	B	(B)
Fire setting	2	4	....	....	C	C
Destruction of objects	8	7	0.00	....	C	C
Stealing	4	8	0.90	....	C	C
Symptoms without antisocial acts	24	12	8.45	0.01	B	B

Anxiety; Neurotic Symptoms and Acts.—Negative predictions in these areas are confirmed, but positive predictions on single symptoms are upheld only on diffuse anxiety and irritability. Those on emotion and feeling-tone responsiveness appear oftener in the schizophrenic group, but not significantly so. When neurasthenic responses are combined, and neurotic fear responses likewise, however, the prediction is confirmed. Neurotic acts are more the province of the control group, they being the immediate reason for the child's referral to Bellevue Hospital in many cases. Conversely, the presence of symptoms without such acts, is more the province of the schizophrenic group.

In summary, predictions in this area fare as follows:

	Observed				
Predicted	A	(A)	B	(B)	C
A	0	0	0	0	0
B	0	0	4	1	3
C	0	0	0	0	11

Confirmation is 79%; possible confirmation is 5% more.

TABLE 7.—*Predictions and Results for Social Percepts and Responses*

Item	Incidence: Schizophrenic	Incidence: Control	Chi-Square	*P*	Prediction	Observation
Relation to father						
Rejection and fear	13	12	0.00	....	C	C
Hostility and independence	15	11	0.61	....	C	C
Affection and dependence	12	19	2.40	....	C	C
Withdrawal	6	1	....	....	B	(B)
Relation to mother						
Rejection and fear	14	16	0.06	....	C	C
Hostility and independence	12	9	0.30	....	C	C
Affection and dependence	15	21	1.74	....	C	C
Withdrawal	5	1	....	....	B	(B)
Relation to siblings						
Rejection and fear	6 *	4	1.01	....	C	C
Hostility and independence	15 *	19	0.09	....	C	C
Affection and dependence	5 *	11	0.45	....	C	C
Withdrawal	1	0	....	....	B	C
Relation to peers						
Rejection and fear	22	18	0.67	....	C	C
Hostility and independence	19	24	1.26	....	C	C
Affection and dependence	2	6	....	....	C	C
Withdrawal	22	7	13.06	0.001	B	B
Relation to hospital adults						
Rejection and fear	5	0	....	....	B	B
Hostility and independence	10	4	2.33	....	B	(B)
Affection and dependence	14	25	7.32	0.01	B	B
Withdrawal	16	3	11.08	0.001	B	A
Relation to outside adults						
Rejection and fear	4 †	9 ‡	0.71	....	C	C
Hostility and independence	4 †	5 ‡	0.00	....	C	C
Affection and dependence	5 †	11 ‡	1.00	....	C	C
Withdrawal	4 †	0 ‡	....	....	B	(A)
Withdrawal from parents	11	2	6.29	0.02	B	B
Withdrawal from other adults	20	3	17.10	0.001	B	A
Response in disagreement with percept						
Relation to father	11	2	6.28	0.02	B	B
Relation to mother	13	8	1.17	....	B	C
Relation to siblings	10 *	15	0.00	....	B	C
Relation to peers	9	7	0.08	....	B	C
Relation to hospital adults	16	6	5.80	0.02	B	B
Relation to outside adults	6 †	6 ‡	0.36	....	B	C

* Based on 21 cases only.
† Based on 12 cases.
‡ Based on 16 cases.

Social Percepts and Responses.—The results of recordings in this area may be summarized as follows:

1. Withdrawal characterizes the response of the schizophrenic child to peers, parents, and other adults to a significantly greater extent than it does the nonpsychotic child.

2. Approximately as predicted, some schizophrenic children experience fear and rejection from the hospital adult, a response which may clearly be labeled a misperception. Correspondingly, the overwhelming majority responding positively in the control group is not matched in the schizophrenic group.

3. No significant differences appear in response to siblings.

4. More fittingness of perception of others and response to them are found in the control group, significantly for the adults, particularly the father and the hospital adult.[2]

Response to authority fulfills predictions as to the aspects of withdrawal and compliance except for the school situation. Withdrawal from school (truancy) is found frequently in the control, as well as the schizophrenic, group, while compliance in the schizophrenic group is higher than expected. Predictions on hostility tend to be borne out, and those on passive resistance in general, the incidence being too

TABLE 8.—*Predictions and Results in Response to Authority*

Item	Incidence: Schizophrenic	Incidence: Control	Chi-Square	*P*	Prediction	Observation
Withdrawal (ward)	17	2	15.07	0.001	B	A
Withdrawal (home)	21	6	13.19	0.001	B	B
Withdrawal (school)	14	12	0.07	....	B	C
Hostility (ward)	11	4	3.15	0.10	B	B
Hostility (home)	12	13	0.00	....	C	C
Hostility (school)	11	13	0.07	....	C	C
Passive resistance (ward)	7	3	1.08	....	B	(B)
Passive resistance (home)	7	1	....	....	B	B
Passive resistance (school)	8	2	3.00	0.10	B	B
Compliance (ward) *	6	22	15.08	0.001	B	B
Compliance (home) *	4	15	7.71	0.01	B	B
Compliance (school) *	8	14	2.66	....	C	(B)
Manipulation (ward) *	5	8	0.40	....	B	C
Manipulation (home) *	2	3	....	....	B	C
Manipulation (school) *	0	1	....	....	C	C
Passive resistance (all)	22	6	9.52	0.01	B	B

* Expectation is for a higher incidence in the control group, since these responses are more differentiated and are indicative of more positive relationships.

slight for really adequate single tests for ward, home, and school. Predictions on manipulation are not upheld, and a redefining of this category of response may be indicated.

In summary, predictions on social percepts and responses and on response to authority fare as follows:

	Observed				
Predicted	A	(A)	B	(B)	C
A	0	0	0	0	0
B	3	1	14	4	8
C	0	0	0	1	18

Full confirmation is 65%; possible or partial confirmation is 12%.[3]

Sexual Perception and Expression.—In general, the theory would make no specific predictions in this area. The tendency of the schizophrenic group toward self-expression only and the opposite tendency of the control group offer support to the general picture of withdrawal found in the other social areas.

2. Tables 7 and 8 are set up in terms of nonpathognomonic response in these categories: fittingness of response to perception, compliance, and manipulation.

Intelligence and Scholastic Skills.—Again, the theory would not predict poorer performance by the schizophrenic group as a whole. A wider variability on the intelligence quotient would be predicted, and this is confirmed: The quartile deviation is 60% higher for the schizophrenic group. No significant differences in median reading or arithmetical level appear.

TABLE 9.—*Sexual Perception and Expression*

Item	Incidence		Chi-Square	*P*
	Schizophrenic	Control		
Masturbation	8	7	0.0	....
Obscenity	2	2	....	....
Self-exposure	2	2	....	....
Voyeurism	0	2	....	....
Homosexual act (peer)	2	8	3.00	0.10
Homosexual act (adult)	0	4	....	....
Heterosexual act	1	1	....	....
Identity confusion	2	4	....	....
Identified with feminine role	5	0	....	....
Self-expression only	13	8	0.95	....
Expression with others	3	10	3.53	0.10

TABLE 10.—*Intelligence and Scholastic Skills*

Intelligence Quotient Range	Incidence	
	Schizophrenic	Control
100-109	4	6
90-99	3	6
80-89	8	7
70-79	5	6
60-69	1	5
Under 60	9	0
Median	79.5	84.5
Q. D.	16.5	10.5

Achievement Level	Incidence			
	Reading		Arithmetic	
	Schizophrenic	Control	Schizophrenic	Control
Advanced	0	2	0	1
At grade	1	2	0	2
One year retarded	5	1	4	4
Two years retarded	3	5	1	7
Three years retarded	4	3	3	4
Four years or more retarded	3	4	4	3
Skill undeveloped	8	9	10	4
Under age for skill	2	3	2	3
Not measured	4	1	6	2
Median	4 yr. retardation	4 yr. retardation	No skill	3 yr. retardation

SUMMARY

As a check on specific hypotheses arising from the theory and understanding of childhood schizophrenia developed at Bellevue Hospital, under the leadership of one of us (L. B.), the case records of 30 schizophrenic and 30 nonpsychotic disturbed children were analyzed. One hundred and thirty-eight items were rated and recorded by a team of two psychiatrists, a social worker, and a psychologist. Sources of

information were notes from psychiatric interviews; notes of nurses and ward personnel; physical and psychological examinations, both objective and projective, and interviews with parents. Items were classified in the areas of vasovegetative and motor functioning, body image and self-world perceptions and reality testing, anxiety and neurotic symptoms, social percepts and responses, responses to authority, sex expression, and intellectual functioning. Specific predictions on each item or group of items were made in advance. Statistical confirmation of these was high, full confirmation ranging from 60 to 79%, and full or partial confirmation from 77% to 88% in given areas.

So far as the purposes of this introductory study are concerned, the theory and method of testing it appear highly promising. The confirmation figures yield possibly a minimal estimate of validity of the hypotheses, since categories were necessarily coarse. As the next major steps we contemplate (1) refining and retesting the recordings on a larger population of more recent date in which the original diagnoses have been confirmed by follow-up study, and (2) setting up a standard recording system for current cases for a more systematic checking of major propositions in the theory. On the whole, it seems fair to say that the following characteristics of the process in childhood schizophrenia have been supported by this study:

1. Childhood schizophrenia is characterized by a disturbance in the regulation of maturation processes at both biological and psychological levels.

2. The dominance of tonic-neck-reflex motility is a particularly striking example of the maturational lag and unevenness of development.

3. The schizophrenic child has basic difficulties in boundaries and segregation of physiological and psychological subsystems.

4. The disorder is characterized by its pervading to some extent virtually all major areas of functioning, in contrast to the more specific concentration of symptoms in single areas among neurotic children and those with primary behavior problems.

5. The concept of plasticity characterizes the behavior and organization of the schizophrenic child in virtually all these areas.

NEUROPSYCHIATRIC ASPECTS OF INFANTILE ECZEMA

Special Reference to the Role of Cutaneous Pain Receptors

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KNOWLEDGE about nonallergic aspects of so-called atopic eczemas gleaned by workers in different fields has become very extensive. Unfortunately, the demands of specialization have placed the contributions from several fields into mutual isolation. If there is to be further progress, not only must there be a wider cross-field dissemination of these contributions, but there must, in addition, be an integration of them. Without such an integration it is doubtful whether workers from one field will be able to use properly the findings of workers from another, and the possibility of error from distorted perspectives would also remain unchecked.

In this paper an attempt will be made to provide this type of integration. A kind of natural history of infantile eczema will be presented along with hypotheses to explain each important step, and with citations from the literature of relevant fields bearing on both the natural history and the hypotheses. Much of the paper will be concerned with matters of the physiology and pathology of the skin.

Most of the material discussed should be as relevant to eczema (atopic dermatitis, neurodermatitis, etc.) in older children and adults as it is to the infantile variety. Attempts will be made to indicate instances in which this is not the case.

THE HISTOPATHOLOGY

Controversy exists regarding the theory of the pathogenesis of eczema in matters involving even the visible pathology. Two schools of thought exist, with eminent adherents on each side, and it might be deemed highly presumptuous for me, who am not a histopathologist, to enter into this controversy. However, it is my opinion that the weight of evidence favors one theory, and that this theory, the newer of the two, will gain adherents as it becomes more widely known.

Both schools acknowledge the intraepidermal vesicle as the fundamental lesion of infantile eczema; the controversy concerns the manner in which it is formed. According to one school, vesiculation is due to changes occurring first in the dermis. According to the other school, it is due to primary changes in the epidermis.

A detailed presentation of the first view (dermal changes primary) is given by MacLeod and Muende.[1] In essence, this theory holds that the vesicle of eczema is

From the Institute of Juvenile Research.

1. MacLeod, J. M. H., and Muende, I.: Practical Handbook of the Pathology of the Skin: An Introduction to the Histology, Bacteriology, and Mycology of the Skin, with Special Reference to Technique, Ed. 3, New York, Paul B. Hoeber, Inc., 1948.

the result of a forceful filtration of fluid derived from capillaries in the dermis, the fluid advancing into the epidermis, where it forces apart the prickle cells and rapidly distends the spaces so formed to produce the vesicles.

This widely held theory was subjected to a thoroughgoing criticism by Percival, Drennan, and Dodds.[2] One of their strongest objections was based on the observation that the area occupied by a vesicle must have been represented originally by a large number of cells. They pointed out that it was difficult to conceive that an influx of capillary filtrate from dermal capillaries could have overcome existing intra-epidermal tissue pressure and exerted sufficient hydrostatic pressure to disrupt the normal intercellular cohesion of the rete cells, with the formation of a fluid-containing space of such dimensions, in the absence of other factors. They raised, in addition, several other astute objections, the total effect of which, in my mind, was to disprove the theory of primary dermal changes.

The explanation of vesiculation given by these authors advocates the second theory, i. e., that epidermal changes are primary.

> Multiple localized foci of epidermal necrosis are produced in association with, or as a result of, the allergic process. A physico-chemical force develops in these areas and sucks the adjacent tissue fluid to them, capillary permeability is increased and the filtrate is also pulled to the necrotic areas. The passage of the capillary filtrate through the epidermis to localized points is evidenced by transient intercellular oedema. The commencing localization of this fluid, together with that derived from liquefied epidermal cells in a commencing vesicle, is also responsible for the temporary appearance of intercellular oedema, which is soon replaced by a pool of fluid as the vesicle matures. The increasing hydrostatic pressure within the developing vesicle gradually overcomes the attracting force, and the movement of fluid within the epidermis stops for the time being, the size of the vesicle being limited by the elasticity of its walls and by the surrounding tissue pressure. The entire process is repeated by the development of fresh areas of epidermal necrosis again upsetting the equilibrium of the tissue fluid and capillary filtrate.[3]

Ormsby and Montgomery[4] adhere generally to the first (dermal pathology primary) theory of vesiculation, citing MacLeod's account to some extent. However, they concede that vesiculation is in part due also to intracellular edema and degeneration of epidermal cells.

In the most recent textbook in the field in the English language,[5] the objections of Percival and associates to the prevailing notions of vesicle formation and a presentation of their theory are incorporated.

The view that epidermal changes are primary gains considerable support when account is taken of the careful studies of experimental eczema made by Haxthausen,[6] Rokstad,[7] and Polak and Mom.[8] The last-mentioned investigators obtained histo-

2. Percival, G. H.; Drennan, A. M., and Dodds, T. C.: Atlas of Histopathology of the Skin, Baltimore, Williams & Wilkins Company, 1947.

3. Percival, Drennan, and Dodds,[2] p. 108.

4. Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, Ed. 7, Philadelphia, Lea & Febiger, 1948, pp. 279-280.

5. Lever, W. F.: Histopathology of the Skin, Philadelphia, J. B. Lippincott Company, 1949.

6. Haxthausen, J.: Some Problems Concerning Pathogenesis of Allergic Eczemas Elucidated by Experiments with Dinitrochlorobenzene, Acta dermat.-venereol. **20**:257, 1939.

7. Rokstad, I.: Skin Reactions Caused by Fractions of Oil of Turpentine and Hexanitrodiphenylamine, Acta dermat.-venereol. (Supp. 15) **26**:362, 1946.

8. Polak, M., and Mom, A. M.: Histopathology of Experimental Eczema (Allergic Contact Type Dermatitis) in Man, J. Invest. Dermat. **13**:125, 1949.

logical sections of eczematous lesions in very early phases and found that the process begins intracellularly in the epidermis with the formation of a "primary microscopic vesicle," that vesicle formation is produced by confluence of primary microscopic vesicles, and that spongiosis (intercellular edema in the epidermis) follows the formation of primary microscopic vesicles.

Ormsby and Montgomery [4] studied histopathological changes in the skin from patch tests. As positive patch tests constitute experimentally produced eczemas which may be activating naturally occurring allergic processes, they are especially pertinent to our discussion. In the cases which Montgomery studied, he found that marked vesiculation in the epidermis had apparently taken place so rapidly that the picture was one of pressure bullae with compression of the cells and without evidence of intercellular edema and spongiosis.

These studies refute the assertion made widely (e. g., by Hill,[9] Sweeley,[10] and Ratner [11]) that, as eczema is basically due to an allergic process, the primary process cannot be in the epidermis. These authors reason that allergic processes affect blood vessels primarily and that therefore the pathological changes of eczema must begin in the dermis, which contains blood vessels, rather than in the epidermis, which does not. This opinion was given considerable support by the ingenious experiment of Rich and Follis,[12] in which these investigators were unable to produce the Arthus phenomenon in the center of the cornea of an experimental animal, presumably because the cornea at this point was avascular. However, when the cornea was made vascular in this area, they were able to do so. I can only state that the findings of several observers in studies made on the skin of human beings have indicated beyond a reasonable doubt that an allergic process can be initiated in an avascular tissue.

The objection may be raised, however, that experimental eczemas, in which the contact of the allergen with the skin is made externally, are not the same as atopic dermatitis, in which presumably the contact is internal. Thus, Sulzberger and Wolf [13] state:

> The clinical appearance of some lesions of a topic dermatitis is often similar to, and sometimes identical with, that of acute, subacute, or chronic eczematous (i. e., contact) dermatitis. It is certain, however, that in the characteristic atopic dermatitis of adults, the essential process is not a direct eczematous one. For the cardinal lesion of true eczema—the pathognomonic intraepidermal vesicle—does not constitute a feature of the primary process of atopic dermatitis beyond infancy. . . . After infancy the primary lesion of atopic dermatitis is an edematous and inflammatory process situated beneath the epidermis in the superficial cutis. Any epidermal changes are secondary in the adult forms; and in view of the properties peculiar to infantile skin, it seems possible that the epidermal changes in infants are also, in most instances, secondary.

On the other hand, Percival, Drennan, and Dodds feel that the pathological process in eczema, regardless of age of subject, etiology, or appearance of lesions, is essentially the same in all cases. They note that the disease in individual patients

9. Hill, L. W.: Pathogenesis of Infantile Eczema: Critical Review, J. Allergy **18**:60, 1947.

10. Sweeley, W. J.: Pathogenesis of Atopic Eczema, J. M. Soc. New Jersey **46**:390, 1949.

11. Ratner, B.: Allergy, Anaphylaxis, and Immunotherapy: Basic Principles and Practice, Baltimore, Williams & Wilkins Company, 1943, Chap. 48.

12. Rich, A. R., and Follis, R. H., Jr.: Studies on Site of Sensitivity in Arthus Phenomenon, Bull. Johns Hopkins Hosp. **66**:106, 1940.

13. Sulzberger, M. B., and Wolf, J.: Dermatologic Therapy in General Practice, Chicago, Year Book Publishers, Inc., 1948, Chap. 4, pp. 157-158.

is capable of showing rapid, profound variations in its clinical and histological appearance and that these modifications constitute stages of a single and uniform inflammatory response. Gordon [14] enumerates specific clinical reasons for venturing the same opinion.

It is true that patients with atopic dermatitis usually have negative patch tests. This would seem to argue for basic differences between external (contact) eczema (e. g., experimental eczema) and atopic dermatitis. However, vesicular responses to patch tests have been observed in patients with atopic dermatitis by Montgomery,[4] Peck and Solomon,[15] and Albert and Walzer.[16] Cooke [17] expresses himself most forcefully on this subject. Having found in infants and young children with "atopic" eczema that he never observed an exacerbation of eczema from the ingestion of that foodstuff which gave an immediate wheal reaction on test, and having evaluated the findings of certain studies of contact dermatitis, he was led to the following conclusions:

1. Neurodermatitis of older children and adults is only chronic eczema, and should be so called.

2. Contact-type eczematous dermatitis is an allergy. Eczema of adults, children, and infants, the so-called atopic dermatitis, is also an allergy. The two are immunologically identical.

3. The method by which contact is established is inconsequential, whether it be external or internal. The type of substance, whether protein, oil, resin, or complex organic chemical (so long as it be not a primary irritant) is immaterial also.

4. Patch tests and clinical test by exposure to the antigen are the only methods available today for etiologic diagnosis.

The comments of Rothman [18] on the subject of itching have some pertinence here also. He notes that itching, which, it is to be remembered, is a universal symptom in all forms of atopic dermatitis, arises exclusively in the epidermis. Lichenification of skin (the typical appearance of atopic dermatitis in adults and older children) he feels is the response of the skin to scratching. On this basis it is not necessary to conceive of lichenification as being indicative of a primary pathological process different from the one in infancy.

To sum up our discussion this far, we may say that there is good evidence for believing that the initial lesion in infantile eczema is the destruction of cells in the prickle-cell layer of the epidermis. The dermis also participates in the eczematous process, but its contribution is probably of secondary significance. Infantile eczema often goes on to a chronic form in later life, in which the clinical appearance of the disease is altered. There is good evidence for believing, however, that even then the basic pathological process is the same.

It is on this basis that I shall use certain findings concerning atopic dermatitis of later life to advance the thesis concerning the pathogenesis of infantile eczema.

The rest of this paper will be devoted to attempting to explain how and why the destructive process occurs in the prickle cells of the epidermis.

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14. Gordon, S.: Infantile Eczema, South African M. J. **25**:697, 1951.

15. Peck, S., and Solomon, G.: Eczema of Infancy and Childhood: Contacts as Etiologic Agents, with Particular Reference to Feathers, Am. J. Dis. Child. **46**:1308, 1933.

16. Albert, M., and Walzer, M.: Contact Reactions in Atopy: Incidence of Contact Reactions with Various Allergens, J. Invest. Dermat. **3**:119, 1940.

17. Cooke, R. A.: Consideration of Some Allergy Problems: Allergic Dermatitis (Eczema), J. Allergy **15**:203, 1944.

18. Rothman, S.: Nature of Itching, A. Res. Nerv. & Ment. Dis., Proc. (1942) **23**:110, 1943.

EVIDENCE FOR THE ROLE OF THE NERVOUS SYSTEM

The findings of Spitz [19] and my own observation [20] that infants with eczema are infrequently held and that this factor seems to have a causative effect on infantile eczema suggested that the central nervous system might play a significant role in the pathogenesis of infantile eczema. The view regarding the importance of the central nervous system was expressed long ago by several distinguished dermatologists, Hebra, Hall, Kreibich, and others.

More recent support for this view has come especially from appreciation of the influence of psychologic factors on atopic and other eczemas of obscure origin in children and adults. Studies and reports have been noted in the literature by dermatologists, pediatricians, allergists, and psychiatrists alike. These reports can be broken down as purporting to demonstrate (1) the influence of psychic factors on the onset and course of the disease; (2) the association of typical personality characteristics or of typical emotional conflicts with the disease, and (3) the favorable effects on the disease of psychotherapy or spontaneous changes affecting the psyche of the patients. These categories will be discussed separately.

Reports of the influence of psychic factors on the onset and course of the disease constitute by far the most voluminous literature of these categories. Almost every article dealing with the second and third categories contains also information belonging to the first. Lynch, Hinckley, and Cowan [21] studied 13 patients with atopic dermatitis, 18 to 26 years of age, and 4 patients with late exudative diathesis and found that in almost all cases onset of the eruption or its exacerbations were subject to environmental influence. Dunbar's volume [22] and several recent textbooks on psychosomatic medicine contain fairly good reviews of this subject.

Sulzberger and Goodman [23] feel that there is no evidence that psychologic factors played etiologic roles in eczema, and this view seems to prevail today among the majority of specialists other than psychiatrists. Psychiatrists often do not commit themselves explicitly on this point but seem, for the most part, to imply that they do believe psychic factors may exert a causative influence. Most observers agree that psychic factors can aggravate the disease.

Dr. Rene Spitz has called my attention to the production of eczema in a dog in Pavlov's laboratory by conditioning methods.[24] Confirmation of this work would be a powerful argument in favor of the view that psychological factors can be etiological.

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19. Spitz, R.: The Psychogenic Diseases in Infancy: An Attempt at Their Etiologic Classification, Psychoanalyt. Study Child **6**:255, 1951.

20. Rosenthal, M. J.: A Psychosomatic Study of Infantile Eczema: I. The Mother-Child Relationship, Pediatrics **10**:581, 1952.

21. Lynch, F. W.; Hinckley, R. G., and Cowan, D. W.: Psychosomatic Studies in Dermatology: Psychobiologic Studies of Patients with Atopic Eczema (Disseminated Neurodermatitis), Arch. Dermat. & Syph. **51**:251, 1945.

22. Dunbar, H. F.: Emotions and Bodily Changes: A Survey of Literature on Psychosomatic Interrelationships, 1910-1945, Ed. 3, London, Columbia University Press, 1946.

23. Sulzberger, M. B., and Goodman, J.: Relative Importance of Specific Skin Hypersensitivity in Adult Atopic Dermatitis, J. A. M. A. **106**:1000, 1936.

24. Hediger, H.: Tierdressur als wissenschaftliche Hilfsmethode, Ciba Ztschr. **3**:915, 1935. Luria, A. R.: Die moderne russische Physiologie und die Psychoanalyse, Internat. Ztschr. Psychoanal. **12**:40, 1926.

Of special interest are individual case studies, such as the one reported by Rogerson,[25] which seem to demonstrate dramatically a controlling influence of the "psyche" upon the clinical response of at least some allergic patients. Rogerson's case was that of a boy who "at home, in a difficult environment, was sensitive to fish and certain nuts. His sensitiveness took the form of an outbreak of prurigo when he came in contact with these substances. On one occasion he was given a chip potato that had been fried with fish; the result was an immediate outburst of urticaria and prurigo. The element of suggestion could not have been important here since he was not aware of the presence of fish. When he was away at a convalescent home, happy and free from anxiety, he was able to eat fish of all kinds with impunity. Some time after his return, however, he was again unable to eat fish."

Rogerson [25] and Stokes [26] independently found that a majority of children with eczema showed excessive motor activity, an unusual amount of anxiety, and pronounced irritability and aggressiveness. These findings were essentially confirmed by Williams.[27] Other studies of typical personality characteristics of patients with atopic eczema have been made by Greenhill and Finesinger,[28] Miller,[29] Walsh and Kierland,[30] Deutsch and Nadell,[31] Lynch and associates,[21] and Kepecs and associates.[32] Miller and Baruch [33] and Harris and associates [34] found typical personality characteristics in allergic children.

These studies are not entirely in agreement with one another as to what the typical characteristics are, and this fact certainly minimizes the significance of such studies for our purposes. On the other hand, many of these studies are complementary, rather than contradictory, highlighting one aspect of the personality rather than another. Some apparent differences may also be due to the difference in age groups in the populations used. It seems quite possible, for example, that the prepubertal child with atopic eczema is typically exhibitionistic,[34] whereas after puberty a change in behavior occurs to make him shy and withdrawn.[32]

That these personality characteristics, so far as they suggest neurotic patterns, cannot entirely be explained as responses of the patients to the unpleasant symptoms

25. Rogerson, C. H.: The Psychological Factors in Asthma-Prurigo, Quart. J. Med. **6**:367, 1937.

26. Stokes, J. H.: The Personality Factors in Psychoneurogenous Reactions of the Skin, Arch. Dermat. & Syph. **42**:780, 1940.

27. Williams, D. H.: Management of Atopic Dermatitis in Children: Control of the Maternal Rejection Factor, A. M. A. Arch. Dermat. & Syph. **63**:545, 1951.

28. Greenhill, M. H., and Finesinger, J. E.: Neurotic Symptoms and Emotional Factors in Atopic Dermatitis, Arch. Dermat. & Syph. **46**:187, 1942.

29. Miller, cited by MacKenna, R. M. B.: Psychosomatic Factors in Cutaneous Disease, Lancet **2**:679, 1944.

30. Walsh, M. N., and Kierland, R. R.: Psychotherapy in the Treatment of Neurodermatitis, Proc. Staff Meet., Mayo Clin. **22**:578, 1947.

31. Deutsch, F., and Nadell, R.: Psychosomatic Aspects of Dermatology with Special Consideration of Allergic Phenomena, Nerv. Child **5**:339, 1946.

32. Kepecs, J. G.; Rabin, A., and Robin, M.: Atopic Dermatitis: A Clinical Psychiatric Study, Psychosom. Med. **13**:1, 1951.

33. Miller, H., and Baruch, D. W.: A Study of Hostility in Allergic Children, Am. J. Orthopsychiat. **20**:506, 1950.

34. Harris, I. D.; Rapoport, L.; Rynerson, M. A., and Samter, M.: Observations on Asthmatic Children, Am. J. Orthopsychiat. **20**:490, 1950.

of the disease itself is suggested by my findings [20] and by the therapeutic effectiveness of favorable emotional changes on the skin disease. Particularly impressive are the results of Williams,[27] who brought about prompt and significant improvements in the eczemas of many infants and children by psychotherapy with their mothers. Reports of therapeutic success following improvements in the emotional status of older child and adult patients have been made by Rogerson,[25] Bartemeier,[35] Ackerman,[36] Miller,[37] Watt,[38] Lewis and Cormia,[39] Wittkower and Edgell,[40] and others.

Brunsting [41] represents a growing trend of opinion among clinicians in stating that "when [atopic dermatitis] occurs in childhood . . . it often is more important to treat the parent than the little patient himself. Affected children and adolescents are usually overstimulated and overambitious, and the management involves more than the care of the skin itself." Ormsby and Montgomery [42] comment:

> It has been our experience also that neurogenic and neuropsychiatric factors may be of great etiologic significance in many cases (of eczema in childhood).

Becker [43] is well known for his advocacy of this point of view.

Neurological evidence is also pertinent, as will be brought out much more fully in succeeding sections. Here, I should like to mention, however, the experiments of Bereston,[44] who found that the intensity of eczematous contact dermatitis experimentally produced was greater on the neurologically normal parts of the body than on affected parts in both hemiplegic and paraplegic patients. Corresponding clinically to these findings are cases of eczema that cleared up on the neurologically involved side only when an acute lesion, such as thrombus, developed in the brain stem.[45]

Finally, one recalls the brilliant research led by Selye,[46] which places eczema among the diseases due to stress, a theory which has recently led to dramatic therapeutic success in providing a rationale for treatment of the disease with cortisone and corticotropin.

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35. Bartemeier, L.: A Psychoanalytic Study of a Case of Chronic Exudative Dermatitis, Psychoanalyt. Quart. **7**:216, 1938.

36. Ackerman, N. W.: Personality Factors in Neurodermatitis: A Case Study, Psychosom. Med. **1**:366, 1939.

37. Miller, M. L.: A Psychological Study of a Case of Eczema and a Case of Neurodermatitis, Psychosom. Med. **4**:82, 1942.

38. Watt, A. W.: Psychological Factors in the Etiology of Certain Skin Diseases, Brit. J. Dermat. **59**:13, 1947.

39. Lewis, G. M., and Cormia, F. E.: Office Management of the Neurodermatoses, New York J. Med. **47**:1889, 1947.

40. Wittkower, E., and Edgell, P. E.: Eczema: A Psychosomatic Study, A. M. A. Arch. Dermat. & Syph. **63**:207, 1951.

41. Brunsting, L. A.: Management of Common Skin Diseases, J. Oklahoma M. A. **39**:47, 1946.

42. Ormsby and Montgomery,[4] p. 277.

43. Becker, S. W., and Obermayer, M. E.: Modern Dermatology and Syphilology, Ed. 2, Philadelphia, J. B. Lippincott Company, 1947.

44. Bereston, E. S.: Certain Effects of Central Nervous System Lesions upon Cutaneous Reactions, J. Invest. Dermat. **6**:75, 1945.

45. McCulloch, W. S.: Personal communication to the author.

46. (*a*) Selye, H.: The Physiology and Pathology of Exposure to Stress, Montreal, Acta endocrinologica, Inc. 1950, p. 738. (*b*) Sternberg, T. H., and Zimmerman, M. C.: Stress Studies in the Eczema-Asthma-Hay-Fever Diathesis, A. M. A. Arch. Dermat. & Syph. **65**:392, 1952.

EVIDENCE FOR INVOLVEMENT OF PAIN-FIBER TERMINALS

In the preceding section of the paper, evidence was presented which suggested that in many cases the nervous system plays an important etiologic role in the pathogenesis of eczema. Recalling that the first visible step in the process is the destruction of cells of the prickle-cell layer, one notes that but two elements of the nervous system permeate this tissue: the fibers and receptors of sensory nerves subserving the sensation of pain, and Merkel's disks (corpuscles), subserving touch sensation.[47]

It is my thesis that the pain-fiber terminals play a very important role in the pathogenesis of the eczema.

The potential importance of the Merkel disks (or other tactile receptors) in this connection appears minimal in view of the following considerations: 1. The disks are most abundant around hair follicles, while atopic lesions are not characteristically follicular. 2. Eczema does not appear on the palms, where touch sensitivity is very great.

The histological nature of the pain receptor in the epidermis has been identified as a free nerve ending lying interposed between prickle cells and immediately adjacent to them.[47] The pain fibers branch repeatedly, mainly in the dermis, and many receptors are derived from each parent fiber (Fig. 1). It is to be noted that the location of these nerve endings is in or very near the area of initial pathology in eczema. Further, the density of pain receptors in the epidermis corresponds approximately to the density of the patches of epidermal necrosis, which are said to be among the first visible signs of pathology in the disease.

Now if pain receptors play a crucial role in the development of the disease, it is logical to infer that they would govern the distribution of lesions. Lesions should be present most commonly in exposed skin areas of high pain sensitivity and least often in covered areas of low pain sensitivity. Let us test this hypothesis.

In accord with the theory is the fact that the face, ears, and neck, the regions where eczema (uncomplicated by seborrhea) oftenest begins, are uncovered areas. Further, the areas of the body which are usually covered by clothing include the areas least often involved in the disease. It is true, however, that the uncovered areas include some regions, e. g., the palms, which are seldom involved and that the covered areas do include some regions which are not infrequently involved. It remains to be seen, then, whether or not these discrepancies can be explained by taking into consideration the factor of pain sensitivity.

Sherman and Sherman [48] found that the face was the most sensitive area of the infant's skin. This would explain some of the discrepancies, e. g., the fact that the face is oftener involved than the legs. More detailed testing of the theory by this means is hampered at this point because it has apparently been impossible to make a detailed study of the variations of pain sensitivity in the different regions of the infant's skin.

47. Woollard, H. H.; Weddell, G., and Harpman, J. A.: Observations on the Neurohistological Basis of Cutaneous Pain, J. Anat. **74**:413, 1940.

48. Sherman, M., and Sherman, I. C.: Sensori-Motor Responses in Infants, J. Comp. & Physiol. Psychol. **5**:53, 1925; Infant Behavior, Comparative Psychology Monographs, No. 4, Baltimore, John Hopkins Press, 1936.

However, a study of pain thresholds in the various regions of the skin in adults was made by Strughold.[49] He concluded that the most important factor influencing pain sensitivity was the thickness of the stratum corneum. The pain sensitivity was lowest in areas where the stratum was thick and highest where the horny layer was thinnest. Since the stratum corneum is poorly developed in most of the regions in the infant's skin, it is clear that Strughold's findings for the adult skin cannot be applied automatically to the skin of infants. It may be noted in passing, however, that the areas of high pain sensitivity found by Strughold include most of the common sites of predilection in the atopic eczemas of older children and adults,

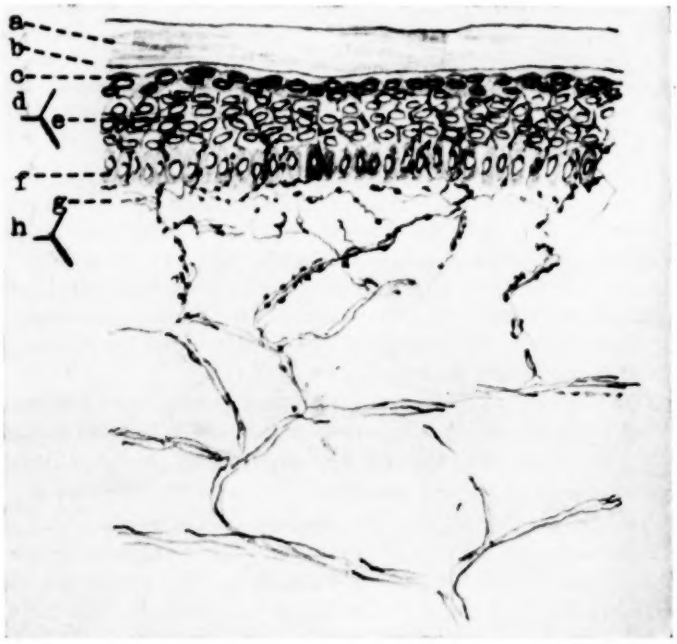

Fig. 1.—Composite drawing showing the arrangement in the skin of the human forearm of nerve fibers and nerve endings subserving pain (redrawn from Woollard, Weddell, and Harpman[47]), in which *a* is the stratum corneum; *b*, the stratum lucidum; *c*, the stratum granulosum; *d*, the prickle-cell layer; *e*, pain receptor in the epidermis; *f*, basal-cell layer; *g*, subepidermal branching of pain fibers, and *h*, dermis.

e. g., the flexural creases, while areas of low pain sensitivity are areas much less frequently involved, e. g., the palms, soles, and mouth. The correlations are striking.

There was one finding of Strughold's which was an exception to the general rule governing sensitivity. This was the surprising fact that pain sensitivity at the tip of the nose (to a less extent, this was true also of the dorsum of the nose) was considerably less than that of other areas of the face. This low sensitivity, however, seemed to be due to a difference in innervation, rather than to a difference of thickness of the stratum corneum. Because of this fact, it occurred to me that infants also might show this peculiarity.

49. Strughold, H.: Über die Dichte und Schwellen der Schmerzpunkte der Epidermis in den verschiedenen Körperregionen, Ztschr. Biol. **80**:367, 1924.

It was theorized that the tip of the nose should as a rule be spared from eczematous involvement and should rarely, if ever, contain the initial or severest lesions. This expectation was fully confirmed. Hall [50] found that in not 1 of the 60 cases studied by him did the rash first appear on the nose, although in 95% the initial lesion was on some part of the head. He adds, further, that the frequent exemption of the skin of this part had struck observers for a long time; it was true that occasionally the nose was affected, but involvement was comparatively rare and usually slight.

Itching is an exceedingly common, if not universal, symptom in infantile eczema. Frequently itching precedes and heralds the appearance of visible pathological changes. It would be interesting, then, to see whether this, too, could be accounted for on the basis of the hypothesis advanced. Unfortunately, controversy still exists regarding the physiological nature of itching. Lewis [51] and others hold that itching is a sensory modality distinct from pain. However, Rothman's theory [18] that itching is weak, protopathic pain seems to be widely accepted. The implication of the pain receptors would be in harmony with my supposition.

Hartman [52] found the face of normal infants more affected by itching powder than the abdomen. This finding is in accord with our hypothesis in that the itching reaction was greater on the area of predilection for eczema than on an area less frequently involved, assuming that a low-itching threshold means a low pain threshold.

Finally, it is of interest that three therapeutic agents of value in many cases of eczema have striking pain and itching anesthetic properties. I have in mind the antihistamines,[53] cortisone, and corticotropin.[54] It is not necessary for the present argument to prove that these agents specifically dull the pain-fiber terminals. So far as I know, this has never been demonstrated. The antihistamines do, however, diminish pain sensitivity in normal, as well as pathological, skin. The suggestion is made that the manner in which they act to raise the pain threshold is, simultaneously, an important reason for their therapeutic benefit.

FORMATION OF VESICLES

The implication of pain fibers in the pathogensis of infantile eczema is confusing until it is recalled that there is evidence for believing that pain fibers function extensively in carrying retrograde stimuli. Since the pain terminals lie immediately

50. Hall, A.: An Inquiry into the Etiology of Infantile Eczema: III. Brit. J. Dermat. **17**:247, 1905.

51. Lewis, T.: Pain, New York, The Macmillan Company, 1942, p. 113.

52. Hartman, cited by Peiper, A.: Die Eigenart der kindlichen Hirntätigkeit, Leipzig, Georg Thieme, 1949, p. 23.

53. Rosenthal, S. R., and Minard, D.: Experiments on Histamine as Chemical Mediator for Cutaneous Pain, J. Exper. Med. **70**:415, 1939. Parrot, J. L.: Sur le mécanisme périphérique de la douleur: Intervention de l'histamine dans le brûlure et le prurit, Compt. rend. Soc. biol. **137**:620, 1943. Kopel, D., and Raubitschek, F.: Inhibition of Intracutaneous Pharmacodynamic Skin Reactions by Intracutaneous Administration of Antihistamine, Dermatologica **97**:319, 1948. Halpern, B. N.; Perrin, G., and Dews, P. P.: Pouvoir anesthésique local de quelques antihistaminiques de synthèse: Relation entre l'action anesthétique et l'action antihistaminique, Semaine hôp. Paris **24**:2561, 1948. Hunter, R. B.: Neoantergen in the Treatment of Urticaria: Report of 14 Cases, Lancet **1**:672, 1947.

54. Lee, R. E., and Pfeiffer, C. C.: Effects of Cortisone and 11-Desoxycortisone on Pain Thresholds in Man, Proc. Soc. Exper. Biol. & Med. **77**:752, 1951.

adjacent to epidermal cells and since they are not encapsulated, it can be seen at once on theoretical grounds that retrograde (antidromic) impulses carried down to pain terminals could affect the functioning of the adjacent epidermal cells. A number of clinical and experimental findings indicate that retrograde impulses can cause destruction of the adjacent cells and thereby initiate vesicle formation. It may be in precisely this manner that the central nervous system influences the skin to aggravate and/or produce eczema.

There is unequivocal clinical evidence that irritative conditions involving the peripheral sensory tracts can produce vesicles. Clinical conditions in which vesicles are produced in this manner include herpes zoster, tabes dorsalis, causalgia, tumors of the spinal cord and dorsal roots, and the status following operative manipulation of these structures (Lewis,[55] Grinker and Bucy,[56] Best and Taylor [57]). It is likely that blistering following hypnotic suggestion is produced in a similar manner.[58]

Incidentally, recent findings that the zoster virus may be recovered from vesicles in that disease does not negate the point under discussion, since vesicles appear also with irritative aseptic conditions. Further, the skin condition in herpes zoster improves dramatically when the affected nerves are blocked by a local anesthetic.[59] Of course, injury to the epidermal cells by the zoster virus would augment the vesiculating influences from the sensory nerves.

Vesicles have never been produced experimentally by stimulating posterior roots, probably, as Lewis [60] suggests, because it has never been possible to maintain the stimulation sufficiently long.

It has never been conclusively shown that the vesicles are produced by irritation of fibers transmitting pain. However, it is known that the irritations must affect the sensory (or at least the dorsal root) components of spinal nerves to produce the effect, and that all the clinical and hypnotic conditions named above are painful. I would add that the intraepidermal location of the vesicles produced in this manner is strong evidence (as discussed in the previous section) that pain-fiber terminals are involved.

The precise manner in which the vesicles are formed in the above-mentioned clinical conditions is not known. Stimulation of the distal ends of cut posterior roots experimentally has been found to have certain significant effects, even though, as mentioned above, vesiculation has not yet been produced in this way. These effects include (1) the production of pain,[61] (2) prolonged increased pain sensitivity

55. Lewis, T.: Blood Vessels of the Human Skin and Their Responses, London, Shaw & Sons, Ltd., 1927, p. 213-214.

56. Grinker, R. R., and Bucy, P. C.: Neurology, Ed. 4, Springfield, Ill., Charles C Thomas, Publisher, 1949, p. 651.

57. Best, C. H., and Taylor, N. B.: The Physiological Basis of Medical Practice: A Text in Applied Physiology, Baltimore, Williams & Wilkins Company, 1950, p. 998.

58. Dunbar,[22] Ullman, M.: Herpes Simplex and Second Degree Burn Induced Under Hypnosis, Am. J. Psychiat. **103**:828, 1947.

59. Findley, T., and Patzer, R.: Treatment of Herpes Zoster by Paravertebral Procaine Block, J. A. M. A. **128**:1217, 1945.

60. Lewis,[51] p. 94.

61. Lewis,[51] p. 79. Pool, J. L., and Brabson, J. A.: Pain on Stimulating the Distal Segment of Divided Peripheral Nerves, J. Neurosurg. **3**:468, 1946.

(hyperalgesia) of the cutaneous nerve territory,[62] and (3) dilatation of the local minute vessels and distant arterioles.[63] These findings are taken as proof that retrograde nerve stimulation can produce skin changes. More specifically, and more relevantly, these changes consist of the liberation from cells of the skin of substances ordinarily liberated by injury of these cells.[64] In this way, experimental findings tend to corroborate the clinical ones, showing that the skin may be damaged by stimuli passing to the skin retrogradely via sensory nerves.

Lewis [55] concludes, after considering a great many findings, that such a state of affairs is not confined to experimental and pathological conditions alone but also occurs normally. It is his belief that the H-substance, which has vasodilating properties, is preformed in the epidermal cells and plays an important role in regulating skin metabolism. He believes that it is being constantly liberated in minute quantities in relatively quiescent periods.[65] Now, this oozing of H-substance, he feels, is in part controlled by antidromic impulses passing along sensory nerves. Lack of such control, he thinks, causes certain cutaneous disturbances, such as glossiness of the skin, that are connected with degeneration of sensory nerves and are comprised in the adjective "trophic."[66]

Similarly, Toennies [67] found in experimental animals that impulses from the spinal cord could and did pass into dorsal root ganglia and thence retrogradely along sensory nerves to the periphery under conditions of normal functioning.

Recently, Frazier and Small [68] stated that it has been discovered that all vesicants, comprising a heterogeneous group of most diverse chemical characteristics, had a chemical property in common; all acted to inhibit utilization of carbohydrates, probably by poisoning hexokinase. They suggest that substances such as histamine and acetylcholine, which are thought to play important roles in wheal production, may act by poisoning enzymes. If their supposition is correct, and applicable to neurogenic vesiculation, the hypothesis advanced here would have to be elaborated as follows: Retrograde stimuli passing down pain fibers in excess of the normal frequency (for reasons to be discussed below) reach the terminals in the epidermis, where a substance (or substances) is liberated which poisons the hexokinase of the adjacent prickle cells and in this manner causes their eventual destruction. The process of vesiculation then follows, according to the hypothesis of Percival and associates. In this connection, the finding of Kwiatkowski [69] that histamine is present in large amounts in peripheral sensory nerves may be very significant.

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62. (*a*) Lewis,[55] p. 79. (*b*) Galletti, R., and Arcangeli, P.: Iperalgesia sperimentale della cute e zone di Head, Rass. neurol. vegetativa **7**:388, 1949; abstracted, Excerpta Med. VIII **3**:2822 1950.

63. (*a*) Lewis,[55] p. 224. (*b*) Gagel, O.: Bau und Leistung des vegetativen Nervensystems, Deutsches Arch. klin. Med. **195**:12, 1949.

64. Lewis,[55] p. 224. Galletti and Arcangeli.[62b] Gagel.[63b] Grósi, P.: Notes on the Mode of Action of Cutaneous Stimuli, Börgyógyász. venereol. szemle; abstracted, Excerpta Med. XIII **3**:1198, 1949.

65. Lewis,[55] pp. 232-233.

66. Lewis,[55] p. 235.

67. Toennies, J. F.: Reflex Discharge from the Spinal Cord over the Dorsal Roots, J. Neurophysiol. **1**:378, 1938.

68. Frazier, C. N., and Small, A. A.: Allergic Dermatitis: View of Its Immunologic and Biochemical Implications, Am. J. Med. **3**:571, 1947.

69. Kwiatkowski, H.: Histamine in Nervous Tissue, J. Physiol. **102**:32, 1943.

THE SPREADING OF LESIONS

We are now in a position to discuss the manner in which eczematous lesions expand.

Usually the disease begins as a small patch in one or two places, and, although new patches may appear later, much of the subsequent pathology of the disease consists of extensions into areas of the skin adjacent to the original patches. This manner of spread is difficult to explain on the basis of the spread of an allergic state alone.

If the allergens are brought to the skin by the blood plasma and lymph, it is hard to understand why large areas of skin are not initially involved simultaneously. Experimental studies on the manner in which sensitization spreads in the epidermis have not yet given a definite answer to the question.[70]

I should like to suggest this following explanation, which is in harmony with known experimental and anatomical facts: Epidermal cells lyse in initial sites as a result of injury from any or all of the following factors: (1) antibody-allergen reaction; (2) injury from sustained states of excitation of pain-receptor nerve endings by antidromic stimulation, and (3) direct injury from external agents. Each form of injury would aggravate the effects of the others.[71] However, there are no good grounds for assuming that allergic mechanisms need always be present.

With the necrosis and lysis of the epidermal cells, there is a spillage of cell contents into the intercellular fluid. This contains, among other things, substances which stimulate pain receptors.[62] Once the pain receptors are stimulated by a local pathologic process, they send impulses centrally to the spinal cord. However, in all probability, they also send impulses antidromically to other pain receptors which come off branches of the same large nerve fiber.[72] The pain receptors which are stimulated in this indirect way may lie over 1 cm. from the receptors originally involved [72a,b]; and if their stimulation is intense and prolonged, they, too, may bring about the necrosis of adjacent epidermal cells. This, then, would account for the spread of pathology within the area of distribution of a single nerve fiber. Successive adjacent areas become involved because of the overlap in the areas of distribution of other nerve fibers.[73] Thus, the spread of epidermal necrosis within the area of distribution of a single nerve fiber causes excitation of pain receptors attached to other nerve fibers which happen to be located within the same area. The excitation of these other pain receptors then spreads the pathology throughout the areas of distribution of their nerve fibers. In this manner, then, it is felt, that eczema progresses in its usual gradual centrifugal manner from an initial site (Fig. 2).

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70. Sulzberger, M. B., and Baer, R. L.: 1939 Yearbook of Dermatology and Syphilology, Chicago, Year Book Publishers, Inc., 1939, pp. 98-99.

71. Gozzano, M.: Allergia e sistema nervoso, Cervello **25**:331, 1949; abstracted, Excerpta Med. VIII **3**:2821, 1950.

72. (*a*) Woollard, Weddell, and Harpman.[47] (*b*) Tower, S. S.: Pain: Definitions and Properties of the Unit for Sensory Reception, A. Res. Nerv. & Ment. Dis., Proc. **23**:16, 1943. (*c*) Harpman, J. A.: Observations on Cutaneous Hyperalgesia, with Notes on Relayed Reactions, Brain **71**:34, 1948.

73. Woollard, Weddell, and Harpman.[47] Galletti and Arcangeli.[62b] Harpman.[72c] Tower.[72b]

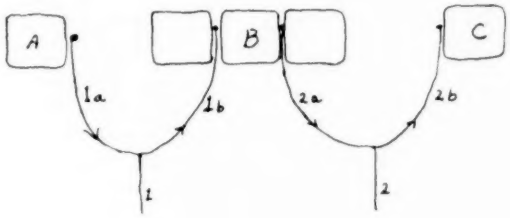
NONALLERGIC PATHOGENIC FACTORS

We have now discussed at some length the nonallergic pathophysiology in cases of infantile eczema. To round out the discussion, we shall now consider the causes of the pathological sequence of events, discussed above. Two factors stand out in importance in relation to the theory proposed: (1) external irritation, and (2) lack of adequate soothing physical contact.

It is not clear that infants with eczema are subjected to an unusual amount of external irritation. Nevertheless, the evidence that external irritation is important is considerable:

1. The skin of eczematous patients, even in uninvolved areas, is hyperirritable to a noxious external stimulus of almost any type, not merely to allergens.[74] One notes in passing that such stimuli are likely to cause pain.

2. The degree of nonspecific skin irritability parallels the severity of the eczema (Weidenfeld, cited by Harris [74c]).



Direction of progression of pathology----→

Fig. 2.—Spread of the eczematous process. Degeneration of cell *A* sends pain impulses along fibril *1a*, a branch of pain fiber *1*. These impulses are also transmitted antidromically along fibril *1b*, another branch of pain fiber *1*. The prolonged excitation of the receptor at the end of fibril *1b* from the antidromic stimulation eventually causes degeneration of cell *B*. The degeneration of cell *B*, in turn, stimulates the receptor at the end of a fibril (*2a*) of another pain fiber (*2*). Impulses passing antidromically within this pain fiber system eventually cause the degeneration of another cell (*C*), which lies outside the territory of the skin covered by fiber *1*.

3. The regions of the normal infant's skin (cheeks and buttocks) which react most intensely to a primary external irritant, phenol in benzene, are sites of predilection of infantile eczema. Areas (thorax and soles) which react less intensely to the irritant are seldom involved in the disease.[75]

4. In almost every case the eruption begins on the head or face, which in the young infant is the part of the skin most exposed to potentially noxious stimuli.[76]

74. (*a*) Bassas Grau, E.: Nota previa sobre unas técnicas personales para el examen funcional de la actividad cutánea, Actas derm-sif. **38**:888, 1947; abstracted, Excerpta Med. XIII **2**:3085, 1948. (*b*) Schreus, H. T.: Zur Pathogenese des exudativen Ekzematoids, Dermat. Wchnschr. **109**:104, 1949. (*c*) Harris, F. G.: Etiology of Eczema, Arch. Dermat. & Syph. **3**:579, 1921. (*d*) Smyth, F. S.: Eczema, in Holt, L. E., and Howland, J.: Holt's Diseases of Infancy and Childhood: A Textbook for the Use of Students and Practitioners, Ed. 11, revised by L. Emmett Holt and Rustin McIntosh, New York, D. Appleton-Century Company, Inc., 1940.

75. Wright, H. P.: Aetiology of Infantile Eczema, Canad. M. A. J. **12**:12, 1922.

76. Hall, A.: An Inquiry into the Etiology of Infantile Eczema: IV. Conclusions, Brit. J. Dermat. **17**:287, 1905.

5. Improvement in infantile eczema frequently follows procedures such as covering the skin with ointment or cotton bandages or putting on arm restraints. These procedures have in common the protecting of the epidermis from unpleasant external stimuli. Similarly, eczema does not occur in intrauterine life, where the fetus is not exposed to such stimuli.

6. The nonspecific irritability of the infant's skin decreases as the infant gets older and could well be in large measure responsible for the fact that eczema so often ceases to be troublesome after the age of 15 or 18 months.[74d]

7. The infant actually does encounter such irritants. In this regard, the observations of Hall [76] are worth quoting at length:

> There are certain surrounding conditions present in infancy which cease, as infancy emerges into childhood. . . . During nine months previous to birth the infant has been surrounded, as to its surface, with a dilute saline solution at a constant temperature of about 100° F., the amniotic fluid. At birth, that constant warm liquid medium is suddenly changed for one which differs from it in three respects; viz., it is gaseous, instead of liquid, its temperature is considerably lowered, and its temperature is no longer constant. To these great changes the infant's neurocutaneous apparatus has to accommodate itself. *As regards its skin*, therefore, the infant at birth changes from a subtropical aquatic existence, to a terrestrial life in a temperate zone.
>
> Its skin, also, for the first time makes acquaintance with various potential irritants—alkalis in the form of soap, micro-organisms which infest the hands and faces of all who handle it, sweat from its mother's skin, the surface of its clothes, and of towels used for drying it. . . . Moreover, it must not be forgotten that an infant, during its first six months of life, has little or no power of localizing or removing any of these irritants. Thus, if its clothes tickle and irritate, it has no power to remove the local irritant; it can merely cry; it is too young to scratch. When it is washed with bad soap which irritates its skin, it cannot point out whether it is thoroughly dried or not. This last point is of considerable importance. We all know that no one can dry our hands or face after washing as efficiently as we can do it ourselves; we also know that inefficient drying in cold weather is a fruitful source of sore hands and face. In an infant efficient drying depends entirely upon the nurse.[77]
>
> And one can readily see why this (repeated chapping and exposure to irritating soap) is more likely to affect the face than the rest of the body in a young infant; because after the general bath, in which the same soap, the same water, and the same inefficient drying, may be used, the body and limbs are at once covered with clothes, so that moisture is absorbed and the clothes prevent evaporation or the contact of cold air with the newly-washed surface. In the case of the face and head this is not so . . . the scalp of the average infant is so scantily provided with hair that for all practical purposes it is hardly more protected than the face.[78]

The objection has been made that, whereas the nonspecific skin reactivity of an infant is greatest on the first day of life and diminishes thereafter, eczema is comparatively uncommon in very young infants, i. e., whose skin reactivity is greatest.[79] This consideration tends to minimize the significance of nonspecific skin reactivity as a factor in eczema. It should be noted, however, that while this progressive decline is characteristic of the reactivity of the skin during infancy, it is not true as regards the sensibility of the skin or nervous system to external stimuli. In the case of sensitivity for pain, for example, Peiper [80] states that newborn infants have a relatively high pain threshold and that this threshold diminishes with increasing age. Thus, it may be that the optimal conditions for the onset of eczema are present when the pain threshold is distinctly lower than that of the newborn, while skin

77. Hall,[76] p. 295-296.

78. Hall,[76] p. 298.

79. Selye,[40a] p. 900.

80. Peiper, A.: Die Eigenart der kindlichen Hirntätigkeit, Leipzig, Georg Thieme, 1949 p. 19.

reactivity is still fairly high, and that it is because such conditions may obtain in the third to the sixth month of life that most cases of infantile eczema begin then.

One might question whether stimuli, such as would arise from damp skin, irritating clothes, etc., would give rise to pain. I feel that they might in the case of infants, especially if their skin was made even more irritable than usual (for reasons to be discussed later). Clinically, there are a number of conditions, e. g., causalgia and tic douloureux, and referred pains of various types in which pain may be aroused by even the mildest external stimuli. Parsons [81] points out that even under normal conditions pain may be aroused by seemingly mild stimuli. Itching, which may involve pain receptors, may at times be precipitated by such gentle stimuli.[18]

As a matter of fact, however, for purposes of this discussion, it is sufficient merely to observe that such stimuli are disagreeable, regardless of whether they stimulate pain receptors. The presence of such an annoying, even if not intrinsically dangerous, environment would make the infant try to alter the situation. Little help would be forthcoming from the mothers of eczematous babies because they are not likely to hold their children.[82] Thus, the baby is deprived of important sources of soothing stimuli for counterbalancing the unpleasant ones.

Spitz [19] apparently made repeated direct observations on the behavior of mothers of eczematous babies and noted an avoidance of physical contact with their infants. He felt that this avoidance represented a fear of their hostile impulses toward the children, but he did not comment on the cause of the hostility.

Rosenthal [20] concluded that these mothers did not cuddle and caress their babies much, or at any rate, for frequent long periods they did not do so. He found that many of them consciously resented the infants as an unwelcome responsibility and interference in their lives, and that their not holding the children often seemed to be an acting out of their rejection of maternal obligations. These findings were based on single short interviews with women from lower economic strata, and as such are subject to a number of obvious limitations. However, trends noted contrasted significantly with those of a control group.

One of the principal effects of the inadequate physical contact with the mothers could well be a need for the infant to rely excessively on internal (physiological) changes for alleviating the discomfort caused by exposure to distressing environmental stimuli. This will be discussed more fully in the following section.

ECZEMA AS AN ADAPTIVE PROCESS

We have now developed a hypothesis to the point of accounting for the immediate mechanisms of vesiculation and spread of lesions. We have also discussed two factors (in the absence of allergy) which are felt to initiate the pathological sequence. There remains to be discussed the manner in which these two etiological factors become effective.

The eczema mechanism, it will be maintained, can best be understood as a purposeful, adaptive process which went wrong. On the basis of considerations already and presently to be cited, nonallergic infantile eczema may be thought of as an attempt by the infant to insulate its skin from injury and unpleasant stimuli.

81. Parsons, J. H.: Adequate Stimuli (with Special Reference to Cutaneous Nerves), Brain **72**:302, 1949.

82. Spitz.[19] Rosenthal.[20]

As a prelude to this topic, it is well to consider this cogent remark of Adrian's [83]:

> It is not difficult to think of exceptions to the rule, but clearly pain, the signal of danger or damage to the body, leads to reactions designed to minimize it, whether they be the simple protective reflexes of the spinal cord or the elaborate planning of the cerebrum involving such operations as the foundation of hospitals and the prosecution of medical research.

It is obvious that the body does not experience painful stimuli passively. In the presence of pain, avoidance or riddance movements (largely inefficient for young infants), with attendant profound homeostatic changes (liberation of epinephrine, etc.), occur. Certain reactions among these render a continued or repeated mild pain less intolerable.

A number of investigators have found that the application of a painful stimulus to the body alters the pain threshold and the subjective evaluation of a subsequent or continued [84] and painful stimulus. The pain threshold is actually raised as a rule,[85] although this may be true only for pain of brief duration and acute sharp, "pricking" quality. There is good evidence that the raising of the threshold depends largely on functional alterations within the spinal cord.[86] However, peripheral changes are also involved.[87]

We shall assert that many cases of eczema represent the tissue alterations consequent to prolonged and exaggerated implementation of the peripheral mechanisms which occur normally after the experiencing of weak pain. When pain is experienced once in nature (e. g., from an insect bite), it is likely to recur or persist unless the offending agent can be gotten rid of. These mechanisms would serve the useful purpose of protecting the tissues from further injury and of mitigating the hurt of the subsequent pain.

Freud felt that the manner in which an organism coped with excitations from the environment was of the utmost importance to it. He wrote in "Beyond the Pleasure Principle" [88]:

> For the living organism protection against stimuli is almost a more important task than reception of stimuli. . . . Beneath the common protective barrier the sense organs, which essentially comprise arrangements for the reception of specific stimuli . . . also possess special arrangements adapted for a fresh protection against an overwhelming amount of stimulus and for warding off unsuitable stimuli.

Following the most widely held theory of pain sensation, that of Lewis [89] and Frey, we shall see in a moment how this might occur. According to them pain

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83. Adrian, E. D.: Pain and Its Problems: Physiology of Pain, Practitioner **158**:76, 1947.

84. von Frey, M.: Schmerz Empfindungen, Tabulae Biol. **2**:282, 1925.

85. (*a*) von Frey.[84] (*b*) Parsons, C. M., and Goetzl, F. R.: Effect of Induced Pain on Pain Threshold, Proc. Soc. Exper. Biol. & Med. **60**:327, 1945. (*c*) Hardy, J. O.; Wolff, H. G., and Goodell, H.: Studies in Pain: A New Method for Measuring Pain Threshold; Observations on Spatial Summation of Pain, J. Clin. Invest. **19**:649, 1940. (*d*) Kunkle, E.; Charles, G.; Armistead, D. C., and Goodell, H.: Experimental Studies on the Spread of Pain, ibid. **27**:545, 1948. (*e*) Fortuyn, J. D.: On Spatial Summation of Sensory Stimuli in Man, Brain **72**:562, 1949. (*f*) Sinclair, D. C.: The Remote Reference of Pain Aroused in the Skin, ibid. **72**:364, 1949.

86. Wolff, H. G., and Hardy, J. D.: On the Nature of Pain, Physiol. Rev. **27**:167, 1947. Kunkle and others.[85d] Fortuyn.[85e]

87. Harpman.[72e] Sinclair.[85f] Lewis, T.: The Nocifensor System of Nerves and Its Reactions (George Halliburton Hume Lecture), Brit. M. J. **1**:431 and 491, 1937.

88. Freud, S.: Beyond the Pleasure Principle, London, Hogarth Press, 1950, p. 30.

89. Lewis,[51] p. 109.

results when, as a result of injury to a cell, the cell releases a substance or substances into the interstitial tissue fluid which excite the pain receptors lying there.

Lewis realized, even before he had fully developed his theory of pain, that the "triple response," the generalized inflammatory response of the skin to any type of injury, had a protective function.[55] He wrote[90]:

> This triple response is propulsive, being directed to the tissue spaces and producing local changes in blood supply and lymph flow requisite to defend the surviving cells from further injury. This increased flow will tend to wash away or dilute injurious substances and will bring leucocytes more quickly through the vessels of the affected region; very possibly it acts further as a necessary preliminary to reparative processes.

Thus, the increase of fluid in the tissue spaces which results when the skin is damaged has a protective function.

Now, although Lewis seems not to have thought of this, even after he had developed his theory of pain, it is apparent that the flooding of the tissue in the triple response would dilute the pain-producing substance liberated by injured cells, as well as the injurious substances which damaged the cells to begin with. By dilution of pain substance, the intensity of the pain sensation would be diminished, for, obviously, the intensity of the pain sensation, even to the point of pain not being experienced at all, would be dependent entirely on the concentration, and not on the absolute amount of pain substance in the tissue. Confirmatory evidence of this thesis seems to be present in the report of Barbieri,[91] who claimed to be able to produce local anesthesia by injecting distilled water intradermally. Again, Seeberg[92] found that the greater the edema of the skin, the faster was the absorption and the less the reaction to an irritating substance administered intradermally.

It is quite possible, then, that the local flooding of tissues is an important part of the mechanism whereby the experiencing of pain raises the threshold for a subsequent painful stimulus.

Further understanding of the adaptive nature of eczema requires a detailed consideration of the phenomenon of hyperalgesic skin. This syndrome is characterized by lowering of the pain threshold, at least for the burning type of pain, and by a greatly increased intensity of pain when once it is aroused. In addition, it is significant for our purposes to note that localized edema is a concomitant of the usual hyperalgesia syndrome. In this connection, one has but to reflect on the fact that most clinical states showing the syndrome are inflammatory.

Clinically, patients with this type of skin may experience severe pain from the slightest contact of their skin with bedclothes. It is striking to observe the diligence with which such patients protect their skins from any kind of external stimulus. This suggests that the hyperalgesia, intolerable as it sometimes becomes, has a function. The function would be to protect badly damaged skin or underlying tissues from further injury.

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90. Lewis,[55] p. 116.

91. Barbieri, L. L.: Azione dell'H_2O distillata intradermica "Loco dolenti" nelle neuralgie e in altre offenzioni dolorose, Med. internaz. **56**:128, 1948; abstracted, Excerpta Med. VIII **2**:1731, 1949.

92. Seeberg, G.: Intradermal Reactions of the Delayed Type in Relation to the Absorptive Behavior of the Skin, Including Absorption Studies with Radio-Active Phosphorus Isotope P^{32}, Acta dermat.-venereol. (Supp. 18) **27**:1, 1947.

Now, in cases of slighter injury to the skin, itching, rather than pain, is likely to supervene. Even if one does not fully subscribe to Rothman's [18] theory that itching is simply a weak pain, one cannot ignore the extensive evidence he has marshaled showing that itching appears in instances in which greater provocation would produce pain or in which a painful state is subsiding. Furthermore, the pruritic state (universal in eczema) is, as he has commented, so unpleasant that the organism tends to terminate it either by scratching away an external irritant, if that is the cause of the condition, or by simple scratching of the epidermis, in which case the itching gives rise to pain. The latter condition, in which the epidermis may be denuded, or at least thinned down, is, I remark, a hyperalgesic state. Thus, there are good grounds for thinking of the pruritic state as related to the hyperalgesic one, as being, in fact, a phase of the same reaction.

It may seem confusing at first that pain (injury to the skin) sometimes calls forth a raising of the pain threshold, as was discussed previously, and sometimes a lowering of it (hyperalgesia). Perhaps the type of reaction is largely dependent upon the nature of the injury. The experimental work cited above is concerned with injuries which leave the epidermis little altered and which hence are probably not as severe as some of the clinical conditions giving rise to hyperalgesia. If the epidermis is thinned or denuded, the pain receptors are closer to the surface and the pain threshold falls. Furthermore, the break in the skin would allow the edema fluid to escape and thus might seriously impair the dilution mechanism. These matters will be considered further a little later.

Hyperalgesia of the skin may be produced in several ways, but of great significance for our discussion is the fact that it may be produced by retrograde nerve stimulation [85d] and by external irritation. If the account in this paper regarding the pathogenesis of eczema is correct, it would be necessary to postulate that eczematous skin is hyperalgesic. There is good evidence that this is the case.

The poor tolerance of eczematous skin for even mild irritants, such as ordinary soaps, is a familiar clinical example of their excessive irritability to noxious chemical stimuli. The exacerbation of the disease by scratching and rubbing shows the effect of mildly noxious mechanical stimuli. A lowered threshold to pain in patients with inflammatory disorders of the skin, presumably including eczema, was actually found by Hardy and co-workers.[93]

Edema or weeping is a constant feature in eczema according to all accounts of histopathology. According to several studies, a condition of preedema is present as well in noneczematous portions of the infant's skin.[74d] Besides the evidence that this edema (in vesiculation) could arise from neural influences (cited in previous sections dealing with the effects of retrograde stimuli of sensory nerves), there are the related findings of Kepecs, Robin, and Brunner.[94] These investigators found that the amount of transudation of fluid into artificially created blister bases was strikingly influenced by the emotional state of the (adult) subject.

The aforementioned considerations make it possible to entertain the following bold speculation, namely, that nonallergic eczema is essentially a reaction of the skin

93. Hardy, J. D.; Wolff, H. G., and Goodell, H.: Pain Threshold in Man, A. Res. Nerv. & Ment. Dis., Proc. **23**:1, 1943.

94. Kepecs, J. G.; Robin, M., and Brunner, M. J.: Relationship Between Certain Emotional States and Exudation into the Skin, Psychosom. Med. **13**:10, 1951.

with the hyperalgesia-pruritus syndrome. It differs in appearance from other clinical states showing the syndrome only because of its different etiology. Thus, a striking difference from irritative conditions of posterior root nerves, such as herpes zoster and tabes, lies in its not being limited to the area of distribution of certain affected posterior roots. It differs from a burn which causes damage to all or most cells in the affected epidermis, because the pain receptors are not adjacent to every epidermal prickle cell (Fig. 1) and, hence, in eczema the epidermal necrosis occurs in patches, presumably corresponding to locations containing pain receptors, with the vesicles usually remaining relatively small.

It will now be interesting to see whether or not the hypothesis advanced is consistent with experimental findings in the hyperalgesic syndrome.

Lewis [51] and others have given considerable evidence to support the view that skin becomes hyperalgesic due to a local increase of pain-producing substance in the tissue spaces. If this is true, how can it be that in hyperalgesic skin the threshold for the pricking type (as distinguished from the burning type) of pain might be elevated, as was noted by Bigelow and associates [95] and Potelunas and associates?[96] Here, the dilution hypothesis not only would be consistent but would appear to help reconcile the latter findings with those of the prevalent theory.

If the epidermis (which, according to some investigators,[72b] is the seat of pain of "pricking" quality), although injured, is bathed in edema fluid, the concentration of pain substance there might not differ exceedingly from normal to begin with. Because of the larger volume of sol (edema fluid), an even greater than normal amount of pain substance could conceivably be required to be liberated there before the pain receptors could again become stimulated. This means that a greater injury would have to occur in the epidermis to produce pain; in other words, that the pain threshold in the epidermis might be raised. Furthermore, the edema would probably help to cushion the epidermal cells and pain receptors from direct injury, and this would greatly augment the raising of the pain threshold. Blistering following burns probably functions in a similar way.

This explanation is supported by another finding of Bigelow and colleagues. When hyperalgesia was experimentally produced in normal subjects by means of occlusion of the circulation in the upper arm, there was observed a slight fall in pricking-pain threshold during the first 10 minutes, and only after this period did it begin to rise. According to the explanation given above, this would be expected, for immediately after an injury to the skin there would have to be a period when the concentration of pain substance in the epidermis would be increased. This is so because there would have to be a period preceding the dilution of pain substances (and insulating of tissue elements) by fluid (derived mainly from the dermis) during which the pain threshold would fall. During this period it would take less than normal increments of pain substance to raise the concentration of the substance to a point where pain receptors would be stimulated.

I stated in the section on external irritation that it was not necessary (for the sake of the theory) to maintain that the skin of the eczematous infant had initially

95. Bigelow, N.; Harrison, I.; Goodell, H., and Wolff, H. G.: Studies on Pain: Quantitative Measurement of Two Pain Sensations of the Skin with Reference to the Nature of the "Hyperalgesia of Peripheral Neuritis," J. Clin. Invest. **24**:503, 1945.

96. Potelunas, C. B.; Meixner, M., and Hardy, J. D.: Measurement of Pain Threshold and Superficial Hyperalgesia in Diseases of the Skin, J. Invest. Dermat. **12**:307, 1949.

endured painful experiences, that one need but grant that the kind of experiences which were singled out could be classed as unpleasant. Recalling the items enumerated by Hall, this much should readily be granted. One could assume, then, that initially the skin has received a number of unpleasant, though not painful, stimuli. These sensations would be mediated by sense receptors subserving the other sensory modalities, i. e., cold, touch, warmth, and pressure.

For the sake of argument, we could take this to mean that just prior to the onset of the eczematous process the skin had not been damaged and that eczema did not arise as a reparative process.

Suppose, then, the infant had to cope specifically with the problem of dulling certain sensations. How might this be accomplished? The answer is that it might do so in exactly the same fashion as that suggested above with reference to pain; that is, retrograde neural stimuli could produce a flooded condition in the dermis (where most of these receptors are found) in the process of drawing fluid to the epidermis, as described by Percival and associates.[2]

Significantly, this dulling does occur in hyperalgesic areas of the skin. A number of investigators have found that in such areas all sense modalities but pain of a burning type are hypesthetic.[72c] This obscure finding, it would seem, could be regarded as a major piece of evidence for the basic speculations entertained here.

The dilution hypothesis does not explain why "burning" pain would not also be dulled by the edema of the skin. However, it should be remembered that the problem of the double-pain response is poorly understood. Until this situation is remedied, the aforementioned limitation in the use of the hypothesis should not properly be considered an objection to the hypothesis itself.

Thus, we may conclude that whether or not the eczema begins with the damaging of the skin by external agencies, eczema is the kind of process which would follow such damage. It is possible that merely the threat of such damage is enough to initiate the whole sequence of events. The events seem designed to protect the skin from further external injury, to facilitate reparative processes, and to minimize the excitations.

It is ironical, but apparently true, that measures designed biologically to defend the organism from injury should themselves be causative in damaging it, although rarely fatally, and that the same measures which are designed to minimize unpleasant stimuli result in eczema in the fiasco of creating hyperalgesia while the threshold is raised only for the bland sensory modalities.

There is a parallel here with allergic mechanisms, which are so closely related to, if not identical with, the protective mechanisms of immunity, but which themselves harm the body.

Now I must attempt to answer a question which the reader may have been asking for some time. Most infants are exposed to the same unpleasant external stimuli; why, then, do not they all have eczema? I shall suggest only a partial answer.

Perhaps constitutional factors, such as would tend to render the nerve elements in the skin more reactive, are of decisive importance. This, however, has never been proved. A factor for which there is evidence is the inadequate amount of soothing physical contact with their mothers that most infants with eczema have received.[82] Because of this fact, we must assume that a much higher proportion than usual of the skin experiences of these infants have been unpleasant. Presumably, these

infants would then have a greater reason for attempting to insulate their skins from the external world. The insulating, of course, would tend to prevent all sensation, good and bad alike. It is true that not all infants who have had inadequate caressing and fondling have eczema,[29] so that other factors, such as constitutional or allergic ones, may be involved in every case. Even so, provided only that the skin was not so hyperesthetic as to prevent the usually soothing skin experiences (encountered when a mother holds her child) from being soothing, the eczema might not have occurred had the mothers of the eczematous children given their infants more cuddling.

I am well aware that in reducing the pathogenic aspects of the mother-child relationship to a matter of skin sensations I am guilty of great oversimplification. Yet, surely, the only way in which emotional problems could cause eczema would be for them to derange the infant's physiology in some manner. Even more specifically, the reason for the development of eczema, and not of some pathological change in another tissue, e. g., the liver, must be that the physiology of the skin has been greatly affected by the defects of the mother-child relationships, while that of the liver has not. On the other hand, not every unwholesome mother-child relationship leads to infantile eczema. Lack of soothing skin contacts seems to be the significant factor in those that do.

It is tempting to introduce into the discussion the complex psychodynamics attributed to infants by the school of Melanie Klein.[97] But the simpler explanations offered here suffice to account for the findings at our present stage of knowledge. The manner in which eczema was produced during conditioning experiments[24] involved tactile, and probably painful, stimuli to the skin of a dog and seems, again, to point to the preeminent role of cutaneous sensations in the pathogenesis of the disease.

In the case of older children and adults, the lack of soothing skin experiences, per se, cannot be an etiologic factor. Such victims of the illness would be able to supply their own pleasant skin experiences if this were all that was needed. However, the skin may, in many cases, for reasons peculiar to their emotional development, come to be selected as a somatic arena for emotional conflicts.

Several psychoanalysts have suspected that the skin of these older patients was behaving symbolically, like the skin of the infants according to the theory presented in this paper. Thus, Kepecs and associates[32] write: "Atopic dermatitis may also express passive desires to have the skin rubbed or stroked." In another paper these authors state[98]:

> The itching which develops as the atopic patient becomes angry appears at least in some instances to be a reaction to an irritating person or situation, as if this were an actual contact irritant to the skin.

English[99] speaks of a "longing expressed in the skin by itching which calls for the soothing hand (the hand which scratches is the soothing hand, temporarily at

97. Klein, M.; Heimann, P.; Isaacs, S., and Riviere, J.: Developments in Psycho-Analysis, London, Hogarth Press, 1952.

98. Kepecs, J. G., and Robin, M.: Life Situations, Emotions, and Atopic Dermatitis, A. Res. Nerv. & Ment. Dis. Proc. **29**:1010, 1949.

99. English, O. S.: Role of Emotion in Disorders of the Skin, Arch. Dermat. & Syph. **60**:1063, 1949.

least)." Groddeck [100] and Jelliffe [101] long ago saw eczema as a longing of the skin for caresssing.

SUMMARY AND CONCLUSIONS

In this paper, findings and hypotheses are presented concerning the pathology and pathogenesis of nonallergic infantile eczema. On the basis of other studies and of the wide applicability of a number of the points made in the present exposition, it is felt that the theory may be applicable to a majority of cases. Also, much of the material discussed may, it is thought, be as relevant to eczema in older children and adults as it is to infants. Nothing discussed in this paper excludes the possibility of coexisting allergies. In cases of eczema in which there is also an allergic factor, the allergic and nonallergic etiologic factors stressed here might be synergistic. On the other hand, no one has ever demonstrated that allergy was a factor in all cases, and the theories of this paper would offer an explanation as to how infantile eczema might develop in the absence of allergy. Eczema has been produced in the experimental animal without using antibody-allergen reactions.

It is asserted that infantile eczema develops as an attempt to shield the most sensitive exposed portions of the infant's skin from real or anticipated injury and, correspondingly, from unpleasant external stimuli. An important reason for initiating the unfortunate adaptive process in the skin, i. e., the pathology, is thought to be the lack of soothing skin experiences in these infants. Their mothers tend to avoid physical contacts with them. For such infants there would be inadequate counterbalancing of unpleasant skin experiences with pleasant ones. A hyperalgesia-pruritus state develops which ultimately would tend to make them avoid most stimuli from the environment.

In the involved areas of the skin, prickle cells in the epidermis are thought to be destroyed by a combination of the effects of injury from external agents and retrograde stimuli passing along pain fibers to terminals immediately adjacent to these cells. The necrosis of these cells leads to the spillage of cell contents into the tissue fluid, which increases the osmotic pressure locally and sucks adjacent tissue fluid to the areas. Capillary permeability is increased in the dermis by the action of epidermal-cell products, and the filtrate is also attracted there. In this manner pools of fluid are formed which lead to the formation of intraepidermal vesicles.

Extension of the pathology may occur because of the stimulation of pain receptors from overlapping nerves in the same skin areas. The impulses sent up these nerves would pass to the periphery at other spots via antidromic impulses along branches of these nerve fibers. The epidermal cells adjacent to the terminals of the latter fibers would necrose, and the process leading to vesiculation would thus be repeated in new areas.

The preeczematous child is thought to react as though he were frequently experiencing or about to experience pain in the skin. Vesiculation would be an adaptive response, since it would tend to protect the tissue elements. It would also dilute pain substances if any were liberated by external injury to epidermal cells.

100. Groddeck, G.: The Book of the It, translated by V. M. E. Collins, New York, Funk & Wagnalls Company, 1950, p. 198.

101. Jelliffe, S. E.: Sketches in Psychosomatic Medicine, Nervous and Mental Disease Monograph 65, New York, Nervous and Mental Disease Monographs, 1939.

In this manner the threshold for "pricking" pain might be elevated. Also, nonpainful sensory modalities which might cause or contribute to unpleasant sensations from the skin would likewise have elevated thresholds.

Nevertheless, clinically, one is impressed not with the sparing of tissues but with the injuring of them, and not with the minimizing of unpleasant sensations but with their intensification. Seemingly, only the laboratory can demonstrate the basically adaptive nature of the eczema.

The explanations offered in this paper are consistent with these statements by men, none of them psychiatrists, who have made outstanding clinical and experimental contributions to our knowledge of the field:

Hall, in 1905 stated:

I venture to suggest that what is generally called eczema, whether it occurs in infants or adults, is a form of reaction or response of the neuro-cutaneous apparatus to external irritation. . . . It seems rational to suppose that such a reaction is intended to serve some purpose, possibly to remove the irritant or to protect the skin surface.[102]

Harris,[74e] in 1921, stated: "Increased irritability of the intraepithelial nerve endings might be followed by itching and vasomotor changes and is probably the basic defect in eczema."

And, in more recent times, Hill stated: "I find myself more and more paying less attention to foods and more to the protection of the skin from external irritation of any sort whatsoever." Jadassohn [103] expresses this opinion even more radically.

Finally, this statement is in the textbook of Sulzberger and Wolf [104]: "The most fruitful etiologic approach is that which considers infantile eczema the result of the maladjustment of the skin to the radical changes of environment which occurred when the baby moved from the uterus into the world."

102. Hall,[76] p. 500.

103. Jadassohn, W.: L'eczema des nourrissons, Ann. pædiat. **165**:173, 1945.

104. Sulzberger and Wolf,[13] p. 173.

USE OF ELECTRIC-CONVULSIVE THERAPY IN MORPHINE, MEPERIDINE, AND RELATED ALKALOID ADDICTIONS

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CURRENT reports indicate that approximately one person in each 3,000 of our population is seriously addicted to drugs of the alkaloid type. The newspapers and popular magazines have recently expressed alarm about this situation, particularly the increasing use of morphine, diacetylmorphine, and meperidine (Demerol) among teen-agers. It is generally believed that the seriously disabled group of drug addicts is continually growing. As a social, economic, and medical problem, drug addiction demands the attention of physicians, challenges their best efforts.

How shall the physician attempt to treat these patients when they are placed in his care? In the medical literature of recent years long-term institutional treatment is generally advocated. Gradual withdrawal of the drug is nearly always presented as the method of choice. The time required by various institutions which attempt treatment of this notoriously obdurate disorder varies considerably but is seldom brief. In a recent report, the United States Public Health Service advised that the addict remain hospitalized at least 135 days.[1]

Most writers on this subject today describe a method of withdrawal by gradual but progressive reduction of dose that extends over approximately two weeks. To alleviate the patient's inevitable physiologic rigors and emotional distresses during withdrawal, some physicians substitute for the habitual opiate a similar, but less familiar, drug. Vogel, Isbell, and Chapman reported the use of methadone during withdrawal of morphine.[2] These observers emphasize the point that drug addicts protest against bearing even a minimal discomfort. Having been weaned from their habitual morphine or diacetylmorphine, they complain bitterly and vociferously as the methadone is, in turn, reduced. Many refuse to go on after having agreed to the plan of treatment proposed. Often the same problems that arose during reduction of the original drug have to be faced again during withdrawal of the substitute.

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1. What to Do with a Drug Addict, report of the Council on Pharmacy and Chemistry, J. A. M. A. **149**:1220-1223 (July 26) 1952.

2. Vogel, V. H.; Isbell, H., and Chapman, K. W.: Present Status of Narcotic Addiction, J. A. M. A. **138**:1019-1026 (Dec. 4) 1948.

Attempts have been made to alleviate the manifestations of withdrawal by administration of corticotropin or cortisone. Recent reports indicate that little or no relief is afforded by these hormones.[3]

Symptoms prominent during withdrawal are uneasiness, irritability, outbursts of temper, spasmodic yawning, sneezing, lacrimation, coryza, hoarseness, hot flashes, chills, vomiting, and diarrhea. Muscular twitchings, pilomotor activity, and headaches are not uncommon. Despondency, sometimes to the point of despair, may be expected. Sometimes delirium, confusion, and other serious psychotic manifestations occur, and suicide may be attempted. Some of the complaints during withdrawal appear to be primarily emotional. Often hysterical or quasihysterical reactions are prominent. Revolt against physical discomfort or emotional stress may take the form of tantrums and raging, weeping protestations. Balked in an imperative desire, many patients exhibit emotional outbursts more or less beyond volitional control.

Most who have had experience in treating addicts agree that in them a true physiologic dependence is established. Having become adjusted to the effects of the drug, often to a daily dose that would promptly kill the ordinary adult, the human organism cannot immediately achieve a new equilibrium without its effects. Withdrawal produces a profound imbalance of function, often vividly distressing, serious, and somatically "real" manifestations of illness. This physical dependence, in contrast with mere emotional craving, distinguishes the habitual user of morphine, dihydromorphinone (Dilaudid), meperidine, or the like, from patients who have become dependent on barbiturates, chloral, or paraldehyde and whose needs are expressed only at a psychic level.

Aside from overt bodily disturbances, which may indeed threaten a patient's life, addicts to the opiates and similar drugs show during withdrawal emotional disorders far more extreme than those habituated to ordinary sedatives. If the patient succeeds in gaining sympathy and obtaining additional drugs for his relief during the ordeal, his symptoms, both physiologic and psychic, often become worse, as though in a contest to upset the plan of treatment. In addition to direct, and often severe, physiologic disturbance, the physician must, therefore, deal with the secondary, emotional exacerbation of these disturbances.

In 1948 we began using electric convulsive treatment to eliminate the adverse manifestations of withdrawal, in an effort to help patients progress through this period without severe emotional and physiologic disturbances. This measure was from the first so successful that we felt it should be brought to the attention of others. Soon afterward, Kalinowski and Hoch [4] reported similarly gratifying results. They also pointed out that years earlier Avery and Campbell [5] had found pentylenetetrazol (Metrazol) shock useful in dealing with this problem. Since the results reported by Kalinowski and Hoch were so regularly confirmed in our experience with electric treatment to eliminate withdrawal manifestations, we felt

3. Fraser, H. F., and Isbell, H.: Failure of Cortisone and ACTH in Treatment of the Morphine Abstinence Syndrome, Ann. Int. Med. **38**:234-238 (Feb.) 1953.

4. (*a*) Kalinowski, L. B., and Hoch, P. H.: Shock Treatments and Other Somatic Procedures in Psychiatry, New York, Grune & Stratton, Inc., 1946, pp. 190-191. (*b*) Kalinowski, L.: Present Status of Electric Shock Therapy, Bull. New York Acad. Med. **25**:541-553 (Sept.) 1949.

5. Avery, L. W., and Campbell, L. K.: Shock Therapy as an Aid to the Withdrawal of Morphine in Addiction, Dis. Nerv. System **2**:333-335 (Oct.) 1941.

sure that all physicians dealing with drug addiction would be encouraged to use this means to spare their patients unnecessary suffering and danger during withdrawal.

It is difficult for us to understand why, during the years since this report was made, so few workers, apparently, have utilized this effective and specific measure to deal with what is otherwise so serious a medical and psychiatric problem. Though Kalinowski and Hoch clearly emphasized the effectiveness of such treatment, they listed it among applications of electric convulsive therapy that have "not yet an established position in psychiatry." [4a] Gallinek has recently expressed the opinion that "E. C. T. is a highly valuable tool so far as management of the withdrawal period [in drug addicts] is concerned." [6] Like Kalinowski and Hoch, he did not, in this report, tabulate his results in statistical form.

Twice during recent months *The Journal of the American Medical Association* has published letters inquiring about the use of electric convulsive therapy for relief of withdrawal symptoms in drug addicts. On each occasion the inquiring physician was advised against using this measure. This negative advice was based on the statement that electric convulsive therapy has not been properly evaluated as a means of relieving withdrawal symptoms.[7] Believing that an adequate evaluation should be made, we offer the report of our experience. It should not be difficult for other workers to test our results and to determine whether or not the procedure referred to briefly by Kalinowski and Hoch "has an established place in psychiatry."

The patient to whom we first administered electric convulsive therapy, in 1948, for withdrawal symptoms was a white man aged 28. He had been discharged from the paratroopers for severe addiction and persistent irresponsibility. While recuperating from a war wound four years previously, he had begun the use of drugs. Since that time he had smoked marijuana, drunk paregoric (camphorated opium tincture), and taken hypodermically dihydromorphinone, or intravenously meperidine, and morphine. The demand for drugs was constant and intense. His maladjustment for the last two or three years had been extreme. In addition to drugs, he used whisky to great excess, made no attempt to work, and ran up debts without compunction. His family had to intervene continually and at considerable expense to keep him out of jails. Features of his behavior suggested a psychopathic personality. He had been sent to hospitals for treatment on several occasions, but each time he refused to put up with the distresses experienced when withdrawal symptoms started and left against medical advice. Socially, he had regressed to the level of a Skid Row derelict.

When we admitted him to the hospital, he was taking 1,000 mg. of meperidine hydrochloride daily. He admitted suicidal impulses, expressed despair, and showed other indications of secondary depression.

Influenced by the depressive element in this patient's situation and by the hope that electric convulsive therapy might help us keep him hospitalized long enough for withdrawal to be accomplished, we began electric shock, giving him one treatment daily. A program for progressive decrease in the dose of meperidine was instituted. After three days we were astonished and delighted to find that we were far ahead of schedule in the program of drug reduction. The patient's meperidine requirement had fallen to 50 mg. twice a day. On the fourth day he received another electric convulsive treatment. Though he twice requested a "shot," he appeared to be in no real distress and showed no physiologic signs of withdrawal. Though he received no additional meperidine after the third day, he remained in the hospital for three weeks, expressing no dis-

6. Gallinek, A.: Controversial Indications for Electric Convulsive Therapy, Am. J. Psychiat. **109**:361-365 (Nov.) 1952.

7. Treatment of Drug Addiction, Queries and Minor Notes, J. A. M. A. **150**:1735 (Dec. 27) 1952; Electroshock Not Recommended for Relief of Withdrawal Symptoms, ibid. **151**:1526 (April 25) 1953.

comfort and improving steadily. We have been able to follow this patient since his discharge. It is interesting to note that he has remained free from narcotics, has been accepted back into the Army, and now holds the rank of master sergeant.

Since that time we have seldom given addicts under treatment any of the drug after they enter the hospital. Instead, they are given electric shock treatments, according to an elastic schedule, treatments being administered as indicated, being determined chiefly by the patient's subjective complaints. No physiologic manifestation of withdrawal has appeared to serve as a supplementary indication for determining when a treatment should be given.

The total number and the frequency of treatments vary, of course, with each patient. In cases of severe addiction we often give three or four treatments during the first 24 hours. On the second day, two or three may be necessary. After this, one treatment daily is likely to suffice over a period of several days. Then a single electric shock treatment on alternate days usually keeps the patient free of distress. It is rarely that we find any indication for continuing electric convulsive therapy beyond the second week of hospitalization. Confusion from the treatment, particularly during the early days, seems to be highly desirable. This no doubt plays an important part in combating the psychic or emotional component of the withdrawal reaction. It is to us interesting and impressive that the typical physiologic disorders are regularly and totally abolished.

Is this method a radical or drastic means of treating drug addiction? In the literature one encounters many condemnations of electric shock therapy, in terms that state or imply that it is a destructive, brutal, or even diabolic, procedure.[8] Some critics even give the impression that physicians who use it do so not to benefit the patient but to satisfy their own unconscious, but still malignant, cruelty.[9]

It is our belief that these extreme condemnations are often made by rapt theorists who, apparently committed in quasi religious fealty to some rigid creed of psychodynamics, lack adequate clinical experience with electric shock treatment to evaluate it realistically.

To the sincere critics who so readily announce the discovery of sadism in other physicians we propose three questions:

1. Is it, or is it not, possible for unconscious resistance (prejudice) to develop when a man, however learned, confronts information which he sees, or thinks he sees, will threaten a cherished article of belief on which he has based the major efforts of his life?

2. Would any physician directly and adequately familiar with the protracted and stormy horrors of withdrawal in severe addiction regard it as an act of compassion to withhold what experience had demonstrated would, without additional risk, spare his patient this truly harrowing experience?

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8. London, L. S.: Libido and Delusion, Washington, D. C., Mental Therapy Publications, 1946, p. 134. Fenichel, O.: The Psychoanalytic Theory of Neurosis, New York, W. W. Norton & Company, Inc., 1945. Book Reviews, South. M. J. **38**:704 (Oct.) 1945. Zilboorg, G.: Mind, Medicine and Man, New York, Harcourt, Brace and Company, Inc., 1943, pp. 14-15.

9. Lindner, R. M.: Prescription for Rebellion, New York, Rinehart & Co., Inc., 1952, pp. 47-54.

3. How long would such a physician, finding himself in the role of patient, persist in such a choice?

For us, all three of these questions have a real and serious interest.

Our patients are handled in the psychiatric section of a general hospital, and we have no legal means of holding them against their will. Before we adopted our present method, few addicts remained long enough to be freed from their drugs. Many lacked a full and strong intention of working all the way to abstinence. Apparently, they began treatment with the limited goal of reduction, hoping to regain a lost physiologic responsiveness to their drugs so that smaller, and more readily available, doses would give the effects they desired but, because of progressive habituation, could no longer obtain regularly. These, apparently, did not really seek rehabilitation but wished to regain a lost or diminished capacity to utilize opiates pathologically. With the regular application of electric convulsive therapy, we have, for several years now, been able to complete withdrawal in most cases and send our patients out of the hospital physiologically free of their habituation.

This, of course, does not constitute a full solution of their problem. Many return in time to the drugs. Some, we are pleased to report, like the patient whose case is briefly cited above, prove themselves able to maintain their freedom and health. We do not say that electric convulsive therapy is a full solution to the basic problems of addiction, but we are confident in recommending it as a uniquely effective method of achieving what unquestionably must always remain for every addict the first step toward real recovery. Some patients, finding themselves really free from the vicious cycle, are able to work successfully toward rehabilitation. It has appeared to us that underlying conditions, particularly elements of real depression, are also favorably modified by electric convulsive treatment, and that such modifications may be of lasting value to the patient.

We have rarely found contraindications to electric shock therapy as a method of avoiding withdrawal reactions. We state without hesitation, what we have already implied, that this entirely effective use of electric shock therapy does not increase the risks of treatment. We feel there are good reasons to believe that these risks are, indeed, diminished. No one can deny that, strictly speaking, there is some risk in almost any therapeutic or diagnostic procedure, whether it be the administration of penicillin or pricking the ear lobe to obtain a drop of blood. Nor can it be denied that slight, but literally real, risk lurks, often unnoticed, in almost every decision to withhold a drug or to refrain from a procedure under consideration.

It is our opinion that the usual physiologic stresses of withdrawal are far more likely than electric convulsive therapy to precipitate coronary thrombosis, to diminish organismal resistance to infection, and otherwise to offer slight dangers. However remote it may be considered, the possibility of suicide during the despairs and miseries of withdrawal, and this alone, constitutes a more serious risk to life than the administration of electric convulsive therapy. The complication of skeletal injury from electric convulsive therapy is not to be ignored. This complication can be avoided by the use of succinylcholine, which has proved to be a safe, reliable, and effective agent for producing full muscular relaxation. Our experience with this drug, reported in a paper by Moss and associates, has convinced us that the ordinarily slight hazards of electric convulsive therapy can by its use be virtually

eliminated.[10] The temporary paralysis induced by succinylcholine abolishes all strenuous muscular contractions. Not only the possibility of skeletal injury, but also any strenuous motor activity that might put stress on a damaged heart, is avoided.

Results of Electric Convulsive Therapy in Thirty-Five Drug Addicts

Patient	Drug	Amount per Day	Duration of Addiction	Treatment	No. of Treatments	Time in Hospital, Days	Withdrawal Symptoms	Physical Complications Existing Before Treatment
1	Morphine	3 grains	2 yr.	ECT	10	10	None	Heart and liver disease
2	Morphine	8 grains	20 yr.	ECT	12	27	None	Decompensated heart and asthma
3	Meperidine	1,200 mg.	1½ yr.	ECT	19	13	None	None
4	Meperidine Meperidine and codeine	600 mg. 6 grains	1½ yr.	ECT	9	7	None	Migraine
5	Meperidine	1,200 mg.	1 yr.	ECT	9	9	None	None
6	Meperidine Meperidine and codeine	600 mg. 6 grains	3 yr.	ECT	12	17	None	None
7	Dihydromorphinone	1½ grains	3 mo.	ECT	11	21	None	None
8	Methadone	160 mg.	1 yr.	ECT	3	3	None	None
9	Methadone	100 mg.	6 mo.	ECT	9	10	None	None
10	Morphine	3 grains	1 yr.	ECT	12	23	None	None
11	Morphine Morphine and meperidine	2 grains 600 mg.	5 yr.	ECT	14	27	None	None
12	Morphine	3 grains	3 yr.	ECT	10	11	None	Painful leg stump
13	Codeine	12 grains	5 yr.	ECT	9	8	None	None
14	Morphine	3 grains	1½ yr.	ECT	12	20	None	None
15	Meperidine	1,200 mg.	1 yr.	ECT	14	21	None	None
16	Meperidine	2,400 mg.	2½ yr.	ECT	19	29	None	None
17	Meperidine	1,200 mg.	8 mo.	ECT	12	31	None	None
18	Meperidine Meperidine and codeine	600 mg. 6 grains	1 mo.	ECT	12	21	None	None
19	Morphine	6 grains	3 yr.	ECT	10	18	None	Liver and heart disease
20	Morphine	2 grains	3 mo.	ECT	10	21	None	Heart disease and arteriosclerosis
21	Meperidine	1,500 mg.	3 mo.	ECT	13	21	None	Dislocation, left shoulder
22	Morphine	2 grains	3 yr.	ECT	40	30	None	None
23	Morphine	6 grains	6 yr.	ECT	9	16	None	Myocardial infarction 1 yr. ago
24	Dihydromorphinone	½ grain	6 mo.	ECT	10	14	None	Myocardial infarction 2½ yr. ago
25	Morphine Morphine and codeine	3 grains 3 grains	2 yr.	ECT	12	21	None	None
26	Meperidine Meperidine and bromide	300 mg. Unknown	1 yr.	ECT	10	33	None	None
27	Morphine	2 grains	1 yr.	ECT	14	24	None	None
28	Codeine	6 grains	1 yr.	ECT	10	21	None	None
29	Meperidine	1,200 mg.	2 mo.	ECT	10	21	None	None
30	Codeine	12 grains	1 yr.	ECT	12	21	None	Migraine
31	Morphine, codeine, marijuana Meperidine	Large amounts 1,000 mg.	4 yr.	ECT	18	21	None	None
32	Codeine Codeine and morphine	3 grains 6 grains	6 mo.	ECT	10	21	None	None
33	Morphine	10 grains	2 mo.	ECT	6	6	None	None
34	Meperidine	300 mg.	4 mo.	ECT	10	14	None	Migraine
35	Dihydromorphinone	⅓ grain	3 yr.	ECT	9	11	None	Renal stones

10. Moss, B. F.; Thigpen, C. H., and Robison, W. P.: Report on the Use of Succinyl Choline Dichloride (A Curare-like Drug) in Electroconvulsive Therapy, Am. J. Psychiat. **109**:895-898 (June) 1953.

The apparent lack of statistical evidence to support the value of electric convulsive therapy in drug addiction prompted us to review a series of our cases, approximately one-fourth of those in which we have used this method. The 35 cases (Table) are representative of the entire group we have treated. Withdrawal symptoms have not been observed by us in any of the patients thus treated.

SUMMARY

Electric convulsive therapy has occasionally been mentioned in the literature as a valuable method of treating withdrawal symptoms in cases of drug addiction. In our experience with this measure we have found it uniformly effective. Recently, opinions have been expressed that statistical evidence has not been presented to justify this method. We present the cases summarized in the Table in the hope that others may use a treatment we have found safe and valuable. It is our opinion that additional studies should be made until ample statistical evidence is available to evaluate electric convulsive therapy as a means of alleviating withdrawal symptoms.

PROGNOSIS IN PSYCHIATRY

Results of Psychiatric Treatment

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WHEN A patient has a psychiatric illness, it is important for the family physician to know the prognosis in order to counsel the patient and his family. The prognosis will influence the physician's advice on matters ranging from the type of treatment recommended to the expected financial burden of hospitalization and lost earning power. Knowledge of the efficacy of treatment is desired by the psychiatrist in order to establish more precise indications, avoid inadequate or ill-defined methods of treatment, and select the treatment of choice. Unrealistic attitudes about prognosis are common, with excessive pessimism on the one hand and overoptimism on the other. Furthermore, it is desirable that treatment methods in medicine be under continuous scrutiny and criticism as to their effectiveness so that suggestions and modifications may be developed for the improvement of therapy.

Several thousand studies of the results of various treatments in psychiatry have been published. To review and draw conclusions from these reports is a large and impossible task for the busy practitioner of medicine. Some authors have collected the results for a single therapy or have reviewed at length and in detail the psychiatric treatments for a given diagnostic group. The present study attempts to make as brief, concise, and fair an estimate as possible of the value of various treatment methods for three reactions groups: schizophrenic, affective, and psychoneurotic. These estimates are then compared.

METHODOLOGY

There are many possible sources of error in studies of the response to psychiatric treatment. These may lie in the selection of cases, the diagnosis, the duration and severity of the illness, and economic and social factors. Other errors may result from the selection or absence of controls, variations in treatment procedures, criteria for improvement, length and completeness of follow-up study, and the statistical methodology used in handling the data. Frequently, admissions and discharges for a given period are compared as though they were the same group of patients. These factors may account for discrepancies in the published reports and warrant caution in the basing of conclusions about therapeutic efficacy on any single report.

It seems that a more reliable estimate of response to treatment may be obtained by collecting numerous reports and averaging them, in the hope that individual errors will tend to cancel out. From the literature, studies were selected which best seemed to avoid the basic errors listed above. Various somatic therapies and psychotherapies, as well as nonspecific therapy, have been

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considered for evaluation of the three reaction groups. Statistical averaging and comparison were done when the number of studies was sufficient. When possible, not only the immediate results but also long-term follow-up observations were considered. In virtually all instances only patients classified as "recovered" or "much improved" were utilized in calculating what will be termed the rate of "much improvement."

There are many difficulties in this method. Groups selected for different therapies are not necessarily comparable in prognosis; e. g., lobotomy patients are generally in a chronic stage; insulin-treated patients, in an acute stage. Careful and rather rigorous criteria were used in the selection and handling of data. After it was determined by variance ratios whether the samples selected were homogeneous, the *t*-score statistical method was used unless there was an obvious clinical contraindication to making comparisons. Only a probability of a difference occurring by chance once in 100 times or less (*P*, 0.01) was accepted as "significant," or once in 1,000 (*P*, 0.001) as "highly significant." In the former case, if the groups were nonhomogeneous (i. e., if the variance ratio was significant), the term "probably significant" was used. Where the chance probability was between 1 and 3 in 100 (*P*, 0.01 to 0.03), we have called the results only "possibly significant."

RESULTS

In summary, this study accepted (1) only categories of patients who showed much improvement or had recovered, (2) means obtained from large groups of patients, and (3) strict confidence levels, as just mentioned.

Schizophrenic Reactions.—The average of 14 reports of the rates of recovery and of much improvement for the nonspecific therapy of schizophrenia was 29 ± 10%. This group of patients was treated by hospital routine alone and serves as a control for other types of treatment. For patients who received insulin coma this rate was 44 ± 11%; for those who received electric shock therapy it was 32 ± 12%. Combined therapy, i. e., simultaneous insulin coma and electric shock, yielded an average rate of much improvement of 38 ± 18%, and electronarcosis, a rate of 43 ± 21%. For lobotomized patients the average improvement rate was 27 ± 9%. For psychotherapy, few studies with wide variation yielded a rate of 42 ± 20%.

A comparison of these results demonstrated that for insulin therapy rates for much improvement are highly significantly better than those for nonspecific treatment (*t*, 4.2; *P*, 0.001) and also significantly better than those for electric shock (t, 2.9; P, 0.01). The results with electric shock could not be shown to be significantly better than those for nonspecific hospital treatment, nor could the results of electronarcosis and psychotherapy be validated as better, even though the average rate was about 13% higher with electronarcosis. Other treatments reviewed showed no significant difference, or there were insufficient data for this type of assessment. This was the case for histamine, continuous sleep, corticoid, and carbon dioxide therapy.

So far, results of immediate treatment only have been considered. Comparable follow-up studies on patients receiving various therapies were difficult to obtain because different authors used different periods, which could not be dealt with adequately. It was possible to establish a definite interval of five years and collect sufficient data to estimate a rate for only two categories: patients receiving nonspecific treatment and insulin-treated patients. Five years after treatment the average percentages of patients recovered or much improved were the same for insulin therapy and for nonspecific treatment, namely, 27%.

Affective Psychoses.—The manic-depressive and involutional psychotic were not differentiated because of the difficulties in differential diagnosis and the paucity of

reports assessing these syndromes as separate entities. The group consists almost entirely of depressed patients, as there are few data on treatment of manic reactions.

The nonspecific treatment of the affective psychoses showed a much improvement rate of 58 ± 20%. For electric shock the average rate was 71 ± 10%, and that for lobotomy, 65 ± 11%. The published reports of patients with affective psychosis treated with electronarcosis, intravenous injection of ether, hormones, dinitriles, and cerebral stimulants were insufficient for statistical assessment.

TABLE 1.—*Rates of Recovery and Much Improvement for Schizophrenia with the Various Psychiatric Therapies*

Type of Treatment	Rates: Percent and Standard Deviation	No. of Studies	No. of Patients
Hospitalization alone	29 ± 9.5	14	52,635
Insulin coma	44 ± 10.6	16	6,582
Electric shock	32 ± 11.7	14	2,541*
Combined therapy	38 ± 17.8	4	1,435
Electronarcosis	43 ± 20.6	8	228
Lobotomy	27 ± 8.8	12	2,547
Psychotherapy	42 ± 19.7	8	1,543
Follow-up (5 yr.)			
Hospitalization alone	27 ± 6.3	7	1,760
Insulin coma	27 ± 6.3	6	1,698

Summary of Differences When the Above Scores Are Compared Using the *t*-Score Method of Testing small Samples*

Hospitalization alone						ns
Insulin coma					ns	t 4.2 P 0.001
Electric shock				ns	t 2.9 P 0.01	ns
Combined therapy (electric shock and insulin)			ns	ns	ns	ns
Electronarcosis		ns	ns	ns	ns	t 2.1 P 0.03
Psychotherapy	ns	ns	ns	ns	ns	ns
Follow-up (5 yr.)						
Hospitalization	ns	ns	ns	ns	ns	ns	ns
Insulin coma	ns	ns	ns	ns	ns	t 4.1 P 0.001	ns

The rates with lobotomy show no significant differences when compared with the other treatments, but lobotomy is omitted from the Table as the type of patients is not comparable to that of other treatment groups.

* Here, ns means not significant even at the $P = 0.05$ level.

The average rates were 13% higher for electric shock than for nonspecific therapy, but statistically we could term this difference only as "suggestively significant." On the other hand, only 1 of 17 of the rates for electric shock lay below the median for the control group. Follow-up figures at the five-year interval were too infrequent for statistical assessment.

Psychoneurotic Reactions.—The mean recovery rate and much improvement rate for psychoneurotic patients receiving electric shock therapy, lobotomy, and various psychotherapies were, respectively, 55 ± 15%, 69 ± 10%, and 68 ± 11%. On the basis of a few reports, the effectiveness of carbon dioxide therapy was

55 ± 9%. None of these differences are statistically significant. Other treatments, such as subinsulin coma, use of sedatives, antihistamines, mephenesin (Myanesin), histamine, inhalation agents, and abreactive techniques could not be assessed.

Comparison of the Rates with the Same Therapy for Different Reaction Types.—As expected, affective psychoses have a higher improvement rate than schizophrenia whether nonspecific therapy, electric shock, lobotomy, or electronarcosis is used. Psychoneurotic reactions, likewise, have a higher improvement rate than schizophrenia. Electric shock results in probably significantly higher rates of improvement for the affective psychoses than for the psychoneurotic reactions.

TABLE 2.—*Rates of Recovery and Much Improvement for the Affective Psychoses with the Various Psychiatric Therapies*

Type of Treatment	Rates: Percent and Standard Deviation	No. of Studies	No. of Patients
Hospitalization alone	58 ± 19.5	12	1,934
Electric shock	71 ± 9.6	17	6,551
Lobotomy	65 ± 11.0	7	787
Intravenous ether *	58 ± 20.0	2	77
Electronarcosis *	78 ± 5.6	2	77

None of the differences are statistically significant, but all but one (16 of 17) of the rates for electric shock treatment are higher than the median for the rates with hospitalization alone. The failure of the rate for electric shock to exceed that for hospitalization alone is not due solely to the large standard deviation of the latter group, as the difference is still significant after transformation of the scores to values of t.

* Not statistically assessed because of insufficient reports.

TABLE 3.—*Rates of Recovery and Much Improvement for the Psychoneuroses with the Various Psychiatric Therapies*

Type of Treatment	Rates: Percent and Standard Deviation	No. of Studies	No. of Patients
Electric shock	55 ± 14.6	9	1,061
Lobotomy	49 ± 9.6	4	299
Psychotherapy	68 ± 12.3	14	1,700
Carbon dioxide *	55 ± 9.0	3	230

None of the differences are statistically significant.

* Not statistically assessed because of insufficient reports.

COMMENT

Despite many therapies in use in psychiatry and thousands of published reports on their efficacy, this study warrants only a few decisive conclusions. They may be stated as follows: 1. In schizophrenic reactions, insulin coma therapy is more effective than nonspecific therapy and electric shock. 2. Five years after insulin therapy this difference has disappeared. 3. Schizophrenic reactions respond less well to the therapies assessed than do neurotic and affective reactions. Apparently, electric shock is of value in affective reactions, and electronarcosis, in schizophrenia.

Why are so few conclusions possible in view of extensive experience and research? First, there are inadequacies in the literature available for analysis. For many therapies, such as use of carbon dioxide, hormones, and histamine, not enough articles have been published to permit this type of statistical evaluation. For others, there were such differences in criteria of selection, method of treatment, determina-

tion of improvement, or follow-up as (*a*) to exclude them from this study or (*b*) to produce wide discrepancies in results in terms of improvement rate. An example of the wide variation in reported results is a range of 7 to 84% with psychotherapy of schizophrenia. When there are few studies and wide discrepancies between them, a great difference between the average rates for a control and for a treated group is required for statistical validation. For example, in comparing the rates for electronarcosis with those for nonspecific therapy of schizophrenic patients, we could term as only "suggestive" an apparently large difference of 14%, because the number of electronarcosis studies was small and the rates of improvement ranged from 9 to 69%.

Another problem is that some groups selected for a certain therapy may not be comparable. This is evident with a lobotomy group, in which frequently the treatment is chosen only for patients who have been ill a long time, have a poor prognosis, and have failed to respond to other therapies.

Insulin produces better immediate results in treating the patient with a schizophrenic reaction than does psychiatric hospitalization alone, but five years later this does not appear to be so. However, the interval of freedom from psychosis allows productivity and normal living, frees hospital beds and personnel, saves money, and provides an opportunity for psychotherapeutic intervention. Furthermore, this situation represents a challenge. How can the effectiveness of the curative process in insulin treatment be prolonged? This problem needs much more research. There is also a need to know why electric shock is not of great value for the schizophrenic group as a whole.

In the affective psychoses, patients have a higher recovery rate regardless of the type of treatment; therefore, comparison of recovery rates may be a poor way of assessing the value of this treatment. A better method might be the determination of the length of hospitalization or disability over a long period in a group of patients treated by one method and compared with a matched group treated by another. The true value of electric shock may be in lessening disability, shortening hospitalization, decreasing suffering, and quickening the return to social effectiveness. After electric shock, relapses may be more frequent.

Evaluation of the results of psychotherapy is not at present possible. Reports are few; discrepancies are wide. Much more careful study and reporting of the type of reaction, its severity and chronicity, the precise method used, and the criteria of improvement are needed. Evaluations of the patient before and after treatment by one other than the therapist and by objective means, such as psychological tests, are desirable. The practicing psychiatrist, with his burden of therapeutic work, has little time for this. Money and personnel for research into methods, processes, and evaluation of therapy are greatly needed in psychiatry.

There are many specialized tools in psychiatry, but it is desirable to know more about their application and what seems to be the effective element in each.

SUMMARY

1. There are new methods of therapy, both physiological and psychological, in psychiatry. Many of these are statistically assessed in this study. For some methods of therapy, however, published investigations are insufficient for assessment of their value.

2. Individual reports are very optimistic about the results of these methods. There is indication of at least temporary reversibility from illness to health.

3. This study indicates that insulin coma therapy is immediately more effective in the treatment of schizophrenic patients than is psychiatric hospitalization alone; electronarcosis is probably more effective than hospitalization. Five years after treatment 27% of both the insulin and the nonspecific therapy groups of schizophrenic patients are well or much improved. For affective psychoses the rates of recovery and much improvement with electric shock therapy are suggestively significantly higher than those for nonspecific therapy (71 and 58%, respectively). In the studies reviewed, no type of treatment could be shown to be significantly better than another type for the psychoneuroses.

4. There is a need for more careful scrutiny of methods, processes, criteria, and efficacy of psychiatric treatments. More personnel and money are needed for research in psychiatry.

CONCLUSIONS

Some pertinent impressions formed from experience in evaluating psychiatric therapies may be mentioned.

1. Certain inadequacies in published reports have made it impossible to evaluate some promising new therapies. The value, in statistical terms, of psychoanalysis and such new techniques as those of Sechehaye, Rosen, Whittaker, and Fromm-Reichmann is really not known. The results of carbon dioxide and corticoid therapies and of recent modification of electric shock techniques, for example, have not been assessed.

2. The use of improvement rates has limitations in evaluating a method of therapy. It does not indicate the shortened duration of hospitalization or disability, the decreased discomfort when hospitalization must continue, or the less obvious attentuation of antisocial or self-detrimental behavior patterns.

3. A review of the literature gives one the impression that there is no room for dogmatism with regard to methods of therapy, factors making for the maintenance of remission, and essential elements in the process of therapy.

4. The type of research which studies and categorizes individual treatment methods is apt to lose sight of the multiple aspects or levels of function of the patient. Compartmentalization in study and therapy is all too common. It directs attention too singly to mind, body, or environmental, cultural, and social factors. Modern psychiatry has developed many techniques. A multiple-factor or multiple-level approach to therapy is often indicated. Simultaneous applications of such techniques as insulin therapy, psychotherapy, environmental manipulation, and expression through art might produce significantly better improvement rates than those reported with special emphasis on an individual method of treatment. In insulin therapy, for instance, 66% of patients failed to make a marked improvement. These statistics do not reveal that many of these patients later may respond to therapy of a different type.

5. Statistics reported here offer strong evidence that the process of mental illness is at times reversible and that this reversibility can be enhanced by therapeutic intervention. This points the way to an important field of future research.

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TREATMENT OF EPILEPSY WITH MYSOLINE

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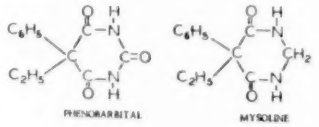
THE PURPOSE of this study was to observe the effects of a new anticonvulsant called Mysoline in a series of 30 epileptic patients treated in the outpatient department of the neurological service of the Mount Sinai Hospital.

In 1952 Bogue and Carrington [1] introduced a new anticonvulsant drug, now known as Mysoline. Chemically, this drug, which is closely related to phenobarbital, is 5-phenyl-5-ethyl-hexahydropyrimidine-4,6-dione. Its formula and its close relationship to phenobarbital are apparent in the figure. It is a white, stable, crystalline



substance, practically tasteless and only lightly soluble in water. It has been described by these authors as having an extremely low toxicity in all species of laboratory animals tested, including monkeys. Mysoline is prescribed in tablet form, each tablet containing 250 mg. of the drug. The daily doses employed in our series of epileptic patients varied from 0.5 to 2.0 gm.

Of the 30 patients, only 2 were treated with Mysoline alone. The remaining 28 epileptics had been under treatment for relatively long periods with various anticonvulsants, singly and in various combinations, without satisfactory results. Of this series of 30 epileptics, 17 had grand mal, 2 had petit mal, 3 had focal seizures, 3 suffered from grand mal and focal seizures combined, 4 had grand mal and psychomotor seizures combined, and 1 suffered from focal, grand mal, petit mal, and attacks of abdominal pain. Only states of automatisms characterized by repetitive, purposeful, but poorly coordinated activity with partial or complete amnesia for the attack were classified as psychomotor attacks. The ages of the patients ranged from 8 to 69 years, and the duration of illness from 1 to 60 years. The anticonvulsants employed included phenobarbital, mephobarbital (Mebaral), diphenylhydantoin (Dilantin), methylphenylethylhydantoin (Mesantoin), trimethadione (Tridione), paramethadione (Paradione), phenacemide (Phenurone), bromides, and chloral hydrate.

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1. Bogue, J. Y., and Carrington, H. C.: To be published.

RESULTS

Grand Mal Only (Table 1).—There were 17 patients with grand mal only. All but two were treated with Mysoline for a period of from 3 to 11 months. For 16 of the patients Mysoline was added to the other anticonvulsants already being administered. For only one patient was Mysoline the only medication employed. Of these 17 patients, 9 have been free from seizures for from 3 to 9 months; 3 have had their seizures greatly reduced in number and frequency, and 1 had the attacks increased in number and frequency. No effect was observed in two patients. In the remaining two patients a toxic reaction followed the ingestion of the first tablet of Mysoline.

TABLE 1.—*Effect of Mysoline on Grand Mal Seizures*

Case No.	Frequency of Seizures with Other Anticonvulsants	Frequency of Seizures with Mysoline Added
1	1/mo.	0 for past 9 mo.
2	1/mo.	0 for past 9 mo.
3	3/mo.	0 for past 8 mo.
4	2/mo.	0 for past 7 mo.
5	1 every 2-3 days	0 for past 6 mo.
6	2/mo.	0 for past 5 mo.
7	6/mo.	0 for past 4 mo.
8	1/mo.	0 for past 3 mo.
9	1/wk.	0 for past 3 mo.
10	4/day to 1 in 2 mo.	2 in past 11 mo.
11	1-7/mo.	2 in past 9 mo.
12	1 every 2-3 wk.	1 in past 5 mo.
13	1 every 2 mo.	No change in past 7 mo.
14	1-3/wk.	No change in past 8 mo.
15	1 every 2-3 mo.	Attacks twice as frequent in past five months—Mysoline discontinued
16*	1 in 2 mo.	Toxic reaction following ingestion of first tablet
17†	1/mo.	Toxic reaction following ingestion of first tablet

* Mysoline only was used, and an acute vestibular syndrome developed.
† Mysoline was added to other anticonvulsants, and an acute vestibular syndrome developed.

These two patients, one of whom was taking Mysoline only, emphatically refused to take any more of this medication.

Focal Seizures Only (Table 2).—Three patients suffered from focal seizures only. In one the seizures had completely disappeared for six months. In the remaining two the seizures had been notably reduced for from 4 to 11 months.

Focal and Grand Mal Seizures Combined (Table 3).—Three patients suffered from both focal and grand mal seizures. In two both focal and grand mal attacks had completely disappeared for five to nine months. The third patient was free of grand mal seizures for four months but continued to have focal attacks, though greatly reduced in number and frequency.

Of the 23 epileptics with focal or grand mal seizures either alone or combined, the attacks in 12 (52%) were completely abolished for from three to nine months. In six (26%) the attacks were notably reduced in number and frequency for an

interval of from 5 to 11 months. In short, 78% of the total number of patients with focal or grand mal epilepsy or a combination of the two types of seizures either were free of attacks or were much improved.

Petit Mal Seizures Only (Table 4).—There were two patients with petit mal seizures only. Both had a marked increase in the number, frequency, and severity of the attacks.

TABLE 2.—*Effect of Mysoline on Focal Seizures*

Case No.	Frequency of Seizures with Other Anticonvulsants	Frequency of Seizures with Mysoline Added
18	1-2 masticatory seizures/mo.	No attacks in past 6 mo.
19	1-2 psychical seizures/day (feeling of remoteness and unreality)	2-3/wk. in past 4 mo.
20*	2-3 masticatory seizures/wk.	1 in past 11 mo.

* Patient has been taking only Mysoline.

TABLE 3.—*Effect of Mysoline on Grand Mal and Focal Seizures*

Case No.	Frequency of Seizures with Other Anticonvulsants	Frequency of Seizures with Mysoline Added
21	1 G.M. or 1 focal seizure every 3-4 wk.	0 G.M.; 0 focal seizures for past 9 mo.
22	1 G.M./mo.; 10 focal seizures a day	0 G.M.; 0 focal seizures for past 5 mo.
23	0 G.M.; 10-12 focal seizures/day	0 G.M.; 2-3 focal seizures/day for past 4 mo.

TABLE 4.—*Effect of Mysoline on Petit Mal Seizures*

Case No.	Frequency of Seizures with Other Anticonvulsants	Frequency of Seizures with Mysoline Added
	Petit Mal Only	
24	Countless attacks daily (blank stare and fluttering of eyelids)	Attacks much more frequent
25	Countless attacks daily (blank stare and fluttering of eyelids)	Attacks much more frequent
	Grand Mal, Petit Mal, Focal Seizures, and Attacks of Abdominal Pain	
26 (age, 10 yr.)	P.M., focal seizures, and attacks of abdominal pain 3-10 daily; no G.M.	G.M., P.M., or attacks of abdominal pain; 1 focal seizure a week during past month; has been taking increasing doses of Mysoline for past 11 mo.

One patient with grand mal, petit mal, focal seizures, and attacks of abdominal pain had been refractory to the commonly known anticonvulsant drugs. With the addition of Mysoline, the patient, while not free of all seizures, was very much improved.

Grand Mal and Psychomotor Seizures (Table 5).—There were four patients with grand mal and psychomotor seizures combined. None of the four patients had had any grand mal seizures in the past 4 to 10 months. However, no effect was observed on the frequency or pattern of the psychomotor seizures.

Toxicity.—Depending upon the dose of Mysoline, the commonest complaints were those of a feeling of drunkenness, drowsiness, lethargy, and difficulty in rousing from sleep. One or all of these complaints appeared in approximately 33% of the patients. In the majority of instances these symptoms were relieved by the

administration of amphetamine sulfate. In some cases these symptoms spontaneously disappeared after the first few days of treatment. In two patients a pruritic papulovesicular eruption developed. The rash promptly subsided on reduction in the dose of Mysoline and did not recur upon resumption of the original doses. In two patients an acute vestibular syndrome developed shortly after the ingestion of the first Mysoline tablet. The reaction consisted of nausea, persistent vomiting, vertigo, ataxia, nystagmus, and, in one case, vasomotor collapse. No blood dyscrasias or abnormal urinary findings were noted.

COMMENT

Handley and Stewart[2] (1952) administered Mysoline to a series of 40 epileptic patients who before its use continued to have grand mal seizures despite all other forms of therapy. The drug was administered to these patients for a period of five to six months, and the authors reported improvement in 80% of patients, with complete freedom from attacks in 37.5%. They noted in a few instances the development of such side-effects as morbilliform rashes, nausea and abdominal discomfort, feelings of mild drunkenness, dizziness, disturbance of accommodation,

TABLE 5.—*Effect of Mysoline on Grand Mal and Psychomotor Seizures*

Case No.	Frequency of Seizures with Other Anticonvulsants	Frequency of Seizures with Mysoline Added
27	0 G.M.; 15-20 psychomotor seizures/mo.	0 G.M.; no change in psychomotor seizures after 5 mo.
28	0 G.M.; 2-4 psychomotor seizures/mo.	0 G.M.; no change in psychomotor seizures after 9 mo.
29	0 G.M.; 2-6 psychomotor seizures/mo.	0 G.M.; no change in psychomotor seizures after 4 mo.
30	1 G.M./wk.; 1 psychomotor seizure/wk.	0 G.M.; no change in psychomotor seizures after 10 mo.

listlessness, and drowsiness. Examination of the urine and blood showed no deviation from the normal. The doses they employed ranged from 0.2 to 2.0 gm. daily.

In our series of 30 epileptics suffering from one or more types of seizures, Mysoline was administered as the only drug to two patients and in combinations with other anticonvulsants to the remaining 28. Twenty-three patients had focal or grand mal seizures or a combination of the two. Of these, 12 (52%) have been free of seizures for the past three to nine months. The seizures in six have been greatly reduced in number and frequency during the past 5 to 11 months. In short, 78% of the patients with grand mal, focal seizures, or grand mal and focal seizures combined improved with Mysoline. In two patients no change was observed, and in one the attacks became more frequent and numerous. Mysoline had no effect on the patients with psychomotor seizures. Of the three patients with petit mal seizures, the addition of Mysoline increased the number and frequency of attacks in the two patients with petit mal only. In the third patient, who had petit mal seizures combined with other types of seizures, the addition of Mysoline produced a marked improvement. However, one of our colleagues (M. B. B.), in a personal communication, has reported improvement in several patients with petit mal whom he has treated with Mysoline in private practice.

2. Handley, R., and Stewart, A. S. R.: Mysoline: A New Drug in the Treatment of Epilepsy, Lancet **1**:742-744 (April 12) 1952.

SUMMARY

In a series of 30 epileptics, Mysoline was added to other anticonvulsants in treatment of 28 patients and was the only drug employed with 2 others.

Mysoline was most effective in patients with grand mal and focal seizures, either alone or combined. In 78% of these patients the condition improved.

No effect on the number or frequency of psychomotor seizures was observed.

Mysoline appears to increase the frequency and number of petit mal seizures.

The commonest side-effects were (*a*) a feeling of drowsiness, drunkenness, and lethargy, relieved in most instances by the addition of amphetamine sulfate; (*b*) a papulovesicular eczematoid eruption, which promptly subsided with decrease in the doses and did not reappear upon resumption of the original dose, and (*c*) an acute vestibular reaction following the ingestion of the first Mysoline tablet and characterized by intense vertigo, nausea, vomiting, severe ataxia, nystagmus, and, in one instance, vasomotor collapse. No blood dyscrasias or abnormal urinary findings were observed.

DIFFERENCES AMONG EPILEPTICS AND BETWEEN EPILEPTICS AND NONEPILEPTICS IN TERMS OF SOME MEMORY AND LEARNING VARIABLES

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THE TRADITIONAL approach to the diagnosis of epilepsy separates epileptics into two groups, those with the idiopathic and those with the symptomatic form. In the first group the seizures are considered to constitute the disease, while in the second group the seizures are assumed to be a symptom of another disorder. Often the basis for differential diagnosis, in both neurology and psychology, has been whether or not the patient showed signs of brain damage or other disorder known to produce convulsions. If he did, his disease was classified as symptomatic, and if not, as idiopathic. This classification of epilepsy has been criticized by Cobb [1] and Nielsen [2] among others, who point out that a diagnosis made by default cannot be a stable one. As better diagnostic methods are conceived the group with idiopathic epilepsy can be expected to shrink. Hence the dichotomy between idiopathic and symptomatic epilepsy would appear to be unstable, and therefore of questionable value. It is difficult to assume that seizures can be a disease in one case and simply a symptom in another. However, some authorities [3] consider that the two groups of epileptics do differ in some essential manner, and certain studies would appear to bear this out.[4]

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2. Nielsen, J. M.: Convulsions of Undetermined Etiology, Arch. Neurol. & Psychiat. **31**:1055-1062, 1934.

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4. (*a*) Bender, L.: A Visual Motor Gestalt Test and Its Clinical Use, Research Monographs, No. 3, American Orthopsychiatric Association, New York, 1938. (*b*) Somerfeld-Ziskind, E., and Ziskind, E.: Effect of Phenobarbital on the Mentality of Epileptic Patients, Arch. Neurol. & Psychiat. **43**:70-79, 1940. (*c*) Yacorzynski, G. K., and Arieff, A. J.: Absence of Deterioration in Patients with Non-Organic Epilepsy, with Special Reference to Bromide Therapy, J. Nerv. & Ment. Dis. **95**:687-697, 1942. (*d*) Arieff, A. J., and Yacorzynsky, G. K.: Deterioration of Patients with Organic Epilepsy, J. Nerv. & Ment. Dis. **96**:47-55, 1942.

Memory function has been frequently mentioned in the psychological literature as defective in epilepsy; and since patients with organic brain damage are generally recognized to have defective memory, this function appeared particularly suitable for the investigation of differences and similarities among epileptics and between epileptics and nonepileptics.

The present study is intended (1) to give information about certain aspects of memory functions in epileptics, that is, (*a*) whether epileptics have a significant deficit on memory tasks as compared with nonepileptics, (*b*) whether patients with idiopathic epilepsy show greater variability in memory performance than do either patients with symptomatic epilepsy or nonepileptics, and (*c*) whether the patients with idiopathic epilepsy are more like the patients with symptomatic epilepsy than like the nonepileptics in terms of memory functions; and (2) to give information about epileptic functioning on some complex perceptual tasks.

METHOD

Three groups of subjects were used in the investigation: (1) 30 patients with idiopathic epilepsy, unselected in terms of type of seizures; (2) 30 patients with symptomatic epilepsy, also unselected in terms of type of seizures, and (3) 30 "normal" subjects, i. e., people without seizures, disease of the central nervous system, or illness diagnosed as psychiatric.

The experimental groups were composed of patients in the epilepsy clinic of the outpatient department of Montefiore Hospital, while the control ("normal") group was composed of patients in surgical, orthopedic, and medical wards of the same hospital. Though no attempt was made to match individual subjects, an effort was made to have roughly comparable groups. Examination by means of *t* tests showed that differences among the groups in age and years of education were not statistically significant.

Diagnosis of the type of epilepsy was established by competent neurologists on the basis of clinical observation, history, and standard medical and laboratory procedures, including electroencephalography. Only those patients were used for whom a definitive diagnosis either of idiopathic or of symptomatic epilepsy was made.

A total of nine procedures was used, administered in the same order to each subject in one session, lasting usually from an hour and a half to two hours. On the first six procedures, which measured memory and learning, both immediate and delayed recall scores were obtained. In every case the interval between the immediate and the delayed testing was filled by the administration of the rest of the battery. The procedures were classified according to type of memory task (rote or meaningful), type of stimulus material (visual, auditory, or tactual), method of memory measurement (recognition, reproduction, recall with stimulus supplied), and simplicity or complexity of task.

Rote Memory Procedures.—I.[5] Hunt-Minnesota Test Designs: The procedure used here followed fairly closely the standard administration procedure for this test except that, instead of the subject's being required to learn all the design pairs, he was given only two immediate and one delayed trial. Score c here was the total number of correct responses on the first two trials, and score d was the number of correct responses on the one delayed trial. (Score c is equal to score a (number correct on first immediate trial) plus score b (number correct on second immediate trial. This notation is used for all procedures.) This procedure uses visual stimulus material, and its memory measurement is recognition.

III. Hunt-Minnesota Word Test: This procedure also was administered in a manner very similar to that of the standard one except for the omission of full learning of the word pairs; again, two immediate and one delayed trial were used. The scores on this task were obtained in the same way as those for Procedure I. This procedure used auditory stimulus material, and its memory measurement was recall to a stimulus.

5. The Roman numerals refer to the order in which the tasks were administered and are used throughout the study as the designation for each task.

V. Tactual Learning: The blindfolded subject was handed a series of five wooden blocks of different shapes. He was asked to tell the examiner the shape of each, and any mistakes he made were corrected. He was then handed each block again and told a color to go with it. He was then required to learn the color of each block while blindfolded. The learning criterion was one correct performance, and the score obtained (l) was the number of trials required for the subject to meet the criterion. The delayed recall score (m) represented the number of trials required for the subject to relearn the colors to meet the criterion. Thus, relearning was the method of memory measurement, and the stimulus material here was tactual. After the relearning trials, the blindfold was removed, and the subject was able to see that the blocks were painted in colors differing from those he had learned, and he was asked to name the colors he had learned for each block. This was done to obtain qualitative data relating to perseveration.

VI. Reproduction of Designs: The design cards from the Wechsler Memory Scale were used. The subject first copied the designs, and a copying score (g) was obtained. Then the original and his copy were removed, and he was required to reproduce them from memory. This provided an immediate recall score (a), and a delayed recall score (d) was obtained when the subject was again asked to reproduce the designs after he had completed the other procedures. The scoring in all cases was according to Wechsler's standards.[6] The memory measurement here was reproduction, and the stimulus material was visual.

Meaningful Memory Procedures.—II. Reading a Story: The first story on the Wechsler Memory Scale was used. The subject was asked to read it aloud, being told that on the completion of his reading he would be asked to recall as much of it as possible. The number of correct memories on the immediate recall was score a. For delayed recall (score d) the subject was simply reminded that he had read a story and was asked to repeat as much of it as he remembered. This procedure used the visual modality, and its memory measurement was reproduction.

IV. Hearing a Story: The second story on the Wechsler Memory Scale was used. The story was read to the subject, thus shifting the stimulus material to the auditory modality. Other than that, the procedure and scoring were identical with those for Procedure II.

Complex Perceptual and Memory Procedures.—VIII. Thurstone Concealed Figures Test: This test was administered as an individual, rather than as a group, test, and the examples were worked out on a question-and-answer basis. A five-minute time limit was employed, and the subject was informed of this limit. Scores obtained on this test were the number attempted (score j), the number of errors (score e), and the number of correct answers (score s). This is a test of complex visual perception.

VII. Complex Auditory Perceptual Task: This is a test constructed for the present study. It is composed of four stories, with a total of 10 questions about them. The subject was told that he would be asked one or more questions and that then a story would be read to him in which the answers to the questions would be given. After the story was completed, he was again asked the questions. The stories were constructed in such a way as to have as many near-correct answers and extra facts as possible. This procedure was considered to measure complex auditory perception, and the only score obtained was the number of correct answers (score a).

Personality Measure.—The Rosenzweig Picture-Frustration test was the only personality measure used. It was administered individually and was scored according to Rosenzweig's system.[7] This test was used in order to have a measure of possible personality factors which may have contributed to the results obtained on the other procedures.

The raw data were tabulated, and for the procedures which used delayed recall as a measure, ratios of the delayed recall score to the immediate recall score were computed, so as to measure relative retention, in addition to simple magnitude of score.

Statistical comparisons were made by means of nonparametric methods.

6. Wechsler, D.: A Standardized Memory Scale for Clinical Use, Provincetown, Mass., The Journal Press, 1945, p. 6.

7. Rosenzweig, S.: The Picture Association Method and Its Application in a Study of Reactions to Frustration, J. Person. **14**:3-23.

For intergroup comparisons, the chi-square test of independence was applied to the numbers of scores falling above and below the common median of the two groups being analyzed at each time.

Intragroup comparisons were made by means of rank-order correlations.

Variability comparisons were made by computing F ratios of significance of differences among variances of the groups on the various procedures.

RESULTS

Statistical treatment of the data indicates that the groups did diverge in their performance on the various procedures and that significant differences among groups exist in this divergence. This is illustrated in the accompanying Table, which presents the chi-square values calculated on the basis of the median test.[8]

The first things apparent in this Table are that there are many significant differences and that some of these differences are very large.

Values for Chi-Square, Corresponding P Values, and Direction of Significance for Intergroup Comparisons of Procedures

	Groups I and II			Groups I and III			Groups II and III		
Procedure *	Chi-Square	*P*	Dir.†	Chi-Square	*P*	Dir.†	Chi-Square	*P*	Dir.†
I e †	3.62	0.05	II < I	0.00	N.S.	.....	5.26	0.08	II < III
I d	0.26	N.S.	I < II	11.40	0.01	I < III	8.52	< 0.01	II < III
II a	6.60	0.01	I < II	32.00+	< 0.01	I < III	13.60	< 0.01	II < III
II d	26.60	< 0.01	I < II	24.00+	< 0.01	I < III	8.07	< 0.01	II < III
III e	3.62	0.05	I < II	6.78	< 0.01	I < III	0.69	N.S.	II < III
III d	6.60	0.01	I < II	15.80	< 0.01	I < III	7.17	< 0.01	II < III
IV a	6.60	0.01	I < II	42.60	< 0.01	I < III	39.90	< 0.01	II < III
IV d	11.30	< 0.01	I < II	40.00+	< 0.01	I < III	40.00	< 0.01	II < III
V l	0.07	N.S.	II < I	4.26	0.04	I < III	13.10	< 0.01	II < III
VI g	8.07	< 0.01	II < I	5.00	0.03	I < III	21.00+	< 0.01	II < III
VI a	6.60	0.01	II < I	45.00	< 0.01	I < III	52.00+	< 0.01	II < III
VI d	6.60	0.01	II < I	52.00+	< 0.01	I < III	60.00	< 0.01	II < III
VII a	2.40	N.S.	II < I	28.00+	< 0.01	I < III	45.00	< 0.01	II < III
VIII j	1.66	N.S.	II < I	0.07	N.S.	I < III	8.00	< 0.01	II < III
VIII s	0.66	N.S.	II < I	1.60	N.S.	I < III	8.00	< 0.01	II < III

* The following notations have been used in the table: a, immediate recall, first trial; b, immediate recall, second trial; e, a plus b; d, delayed recall; g, copying score; l, no. of trials to criterion; j, no. of problems attempted; s, no. of problems correct.

† Direction of significance.

Chart 1 brings out more clearly the nature and extent of these differences. On this graph, the means of the experimental groups for each procedure were translated into standard scores in terms of the mean and sigma of the control-group scores for the same procedure. In this way it was possible to plot the scores for the two experimental groups, i. e., the scores for the epileptic group, in relation to the scores for the control group. To do this, each control-group mean was given a value of 50, and the sigma for that procedure, a value of 10. Then each experimental-group mean was scored in relation to this. For example, if a mean for one experimental group on one procedure score was above the control-group mean a number of points equal to one standard deviation of that control-group mean, the experimental-group mean was given a score of 60. If the experimental-group mean was half a sigma below the control-group mean, the standard score for the experimental group on that test was 45.

8. Moses, L.: The Use of Non-Parametric Methods in Psychological Research, Psychol. Bull. **49**:122-143, 1952.

On the graph, Groups I and II (the epileptic groups) appear to be very similar in their profiles. This similarity was tested statistically by a rank-order correlation, using ranks of these standard scores for each group. Rho (ρ) was 0.74, which is significant at better than the 1% level of probability.[9] This result indicates that the groups with idiopathic and symptomatic epilepsy were similar in their performance on memory procedures.

In order that the groups might be compared further, Charts 2 and 3 were constructed by the same standard-score method as that described for Chart 1. For

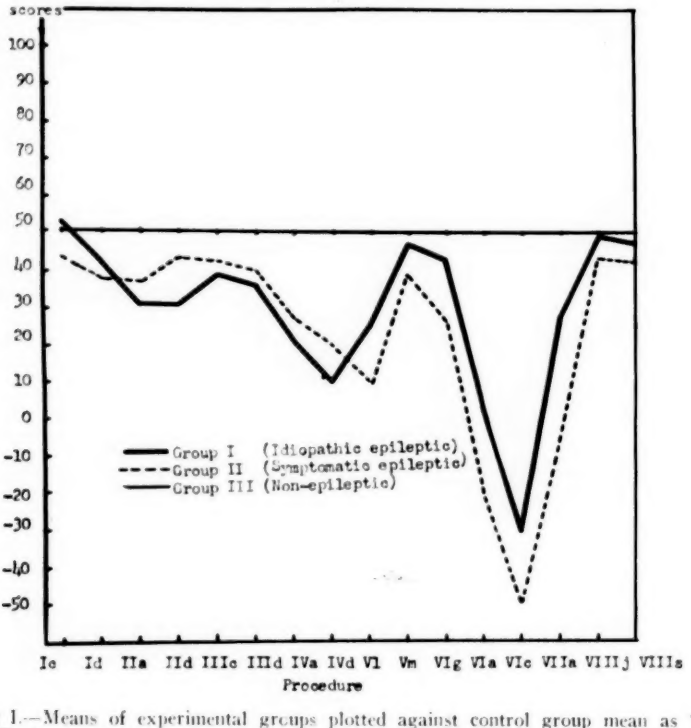

Chart 1.—Means of experimental groups plotted against control group mean as "normal score." Each ten points in score is equal to one standard deviation of the control group.

Chart 2 it was the symptomatic group (Group II), known to be brain-damaged, which provided the norms, and for Chart 3 the idiopathic group (Group I) was the standard.

On Chart 2, Groups I and III would appear to differ considerably in their performance, and the idiopathic group (Group I) is seen to be, with only one exception, inferior to the control group in performance. Again, a comparison of these groups was made by rank-order correlation. Rho was equal to 0.15, which is not significant in terms of the P value.[9]

9. Dixon, W. J., and Massey, F. J.: Introduction to Statistical Analysis, New York, McGraw-Hill Book Company, 1951, p. 261.

In Chart 3, the group with symptomatic epilepsy and the normal group appear to be more similar in performance than are the group with idiopathic epilepsy and the normal group (Chart 2), but not as similar as the two epileptic groups (Chart 1). The rho value calculated for comparison of the group with symptomatic epilepsy and the normal group confirms this impression. The coefficient was 0.40, which is

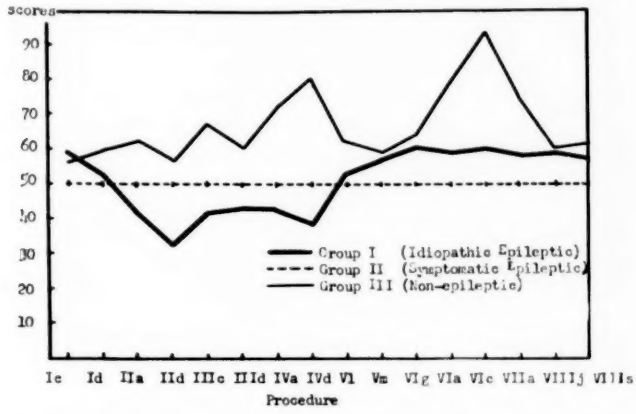

Chart 2.—Means of idiopathic epileptic group and non-epileptic group plotted against known "organic" (symptomatic) group as "norm." Each ten points in score is equal to one standard deviation of the symptomatic group (Group II).

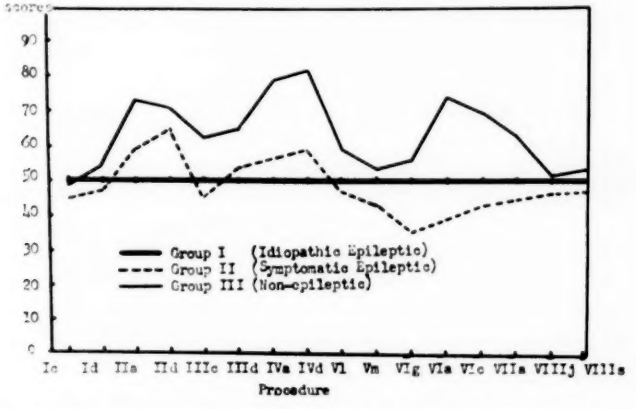

Chart 3.—Means of symptomatic epileptic group and normal group plotted against idiopathic group as "norm." Each ten points in score is equal to one standard deviation of the idiopathic group (Group I).

not significant, but which does fall between the 0.15 found for comparison of the group with idiopathic epilepsy and the normal group and the 0.74 found for comparison of the two epileptic groups.

From these analyses one may say that the two groups of epileptic patients resemble each other more closely in performance on memory tasks than either group

resembles the normal (control) group. However, the curves suggest that the group with symptomatic epilepsy is closer to the normal group than is the group with idiopathic epilepsy. In addition, it may be seen again that both epileptic groups show definite impairment in performance on these memory tasks. In Chart 1 it can be seen that the task on which the two experimental groups deviated most from the control group was VId, i. e., the measure of delayed recall in reproduction of designs. This is a task considered to be exceptionally sensitive to brain damage.[4a]

Further investigation of the pattern of the impaired performance should prove fruitful. Only a limited investigation is possible on the basis of the present data. In Chart 2, however, it may be seen that the group with idiopathic epilepsy differs most from the group with symptomatic epilepsy on Procedure IId, i. e., delayed recall of meaningful material presented to the visual modality. The next greatest difference between the epileptic groups occurs on Procedure IVd, i. e., delayed recall of meaningful material presented to the auditory modality. (Both these differences are statistically significant.) Both these procedures used reproduction as the method of memory measurement. Thus, for future study of patterns in memory impairment among epileptics, tasks which use meaningful stimuli and reproduction measurement appear to be especially worth investigation.

In order that differences in variability might be measured, F ratios were calculated for differences between Group I (idiopathic) and Group II (symptomatic), Groups I and III (normal), and Groups II and III. When the idiopathic group was compared with the symptomatic or the normal group, the idiopathic group showed greater variability than either of the other groups in many instances, but these differences were only occasionally significant. Not infrequently the differences were in the opposite direction. The symptomatic group showed relatively low variability as compared with the normal group; but, again, the direction of the difference was not always the same. No one procedure score or group of scores consistently discriminated among the groups with regard to variability. In short, these data provide no decisive information regarding group variability comparisons.

COMMENT

A problem which must be considered when one is analyzing the results of this study is the possibility of an inflated N through some of the tests measuring the same thing as do others. Thus, some of the differences obtained may relate to the same underlying factors. However, if this error is present, it will not influence the general conclusion of the presence of a deficit in performance on memory tasks in general.

Another problem is the possible contribution of differential fatigability as regards normal and brain-injured persons. To investigate this factor, rank-order correlations were calculated between the order of presentation of the procedures and the rankings of each experimental group. The correlation obtained between Group I and the order of presentation was 0.17; that obtained between Group II and the order of presentation was 0.18, and that obtained between Group III and the order of presentation was —0.12. None of these is significant in terms of the P value; thus, it seems apparent that differences between Group III and the experimental groups cannot be attributed to an effect of fatigue.

Another error which may have disturbed some of the interpretations is the effects of the medication which the epileptics were receiving for control of their seizures.

However, reports in the literature [10] would suggest that differences would not be attributable in any appreciable degree to the effects of drugs. This assumption is borne out by the fact that differences in performance were consistent, while medication and dosage varied considerably. Since the control group was composed of hospital patients, many were given 'sedatives' at night. A t test was computed for differences between the group of control subjects who were taking sedatives and those who were not. The result of this calculation was not statistically significant. Therefore, it is possible to say that, although further study may be profitably attempted on the problem of the effect of drugs on memory tasks, in all probability such effects did not significantly contribute to the present results.

It might be said that the differences obtained are in reality differences in personality organization among the groups. The Rosenzweig Picture-Frustration test was administered to provide a partial check on this factor. The three groups of subjects did not differ significantly in scores on this test, which is said to measure the handling of aggression; so it is improbable that a special personality characteristic relating to expression of aggression toward the examiner or the test situation can account for the differences in memory test performance.

An effort must be made not to "go beyond the data" in any study, more particularly in one of this type. Memory is undoubtedly a complex variable, the component parts of which are hypothesized but not known. Hence, conclusions in this study have stressed "impairment in memory test performance," and it should be stressed that these factors might be the crucial variables in the present study, rather than—or, for example, in addition to—actual physical or chemical interference with intracerebral associative processes. Such a possibility would not, of course, interfere with the negative implication that the present study has for the organic-functional dichotomy. A short attention span is a prominent symptom in brain damage; if, therefore, impaired concentration among epileptics produced the similarity between the two groups of epileptic patients, this similarity might still be based on brain damage or cerebral dysfunction.

In addition, it should be mentioned that the findings of the present study do not dictate any particular theory of the origin of the brain damage or dysfunction postulated in the group with idiopathic epilepsy. Presumably, the cause of the memory defect could be either physiological predisposition or damage produced by the convulsions themselves. The first alternative would seem more logical, in view of the consistency of the differences obtained and the inconsistency of the length of illness or number of convulsions.

Perhaps the most significant implication of the results of the present study would be that patients with idiopathic and patients with symptomatic epilepsy do not appear to constitute really distinct groups. This finding would seem to support the positions

10. Arkola, A. L.: (*a*) An Experimental Study of the Effects of Sodium Amytal upon Performance on the Hunt-Minnesota Test for Organic Brain Damage, J. Clin. Psychol. **3**:392-396, 1947. (*b*) Fetterman, J., and Barnes, M. R.: Serial Studies of the Intelligence of Patients with Epilepsy, Arch. Neurol. & Psychiat. **32**:797-801, 1934. (*c*) Somerfeld-Ziskind and Ziskind.[4b] (*d*) Twitchell-Allen, D.: Educability of a "Deteriorated Epileptic Patient," Arch. Neurol. & Psychiat. **57**:617-622, 1947; (*e*) The Development of Eugene, a 23-Year-Old Boy Isolated by 17 Years of Epileptic Seizures, Psychol. Bull. **37**:524-530, 1940.

held by Cobb,[1] Nielsen,[2] and Lennox [11] that such a disease as "functional" epilepsy (i. e., the seizures themselves considered as the disease, without organic etiology) can not and does not exist. This position is further strengthened by the recognition that memory tests have been used extensively as indicators of brain damage, i. e., of "organicity." Since the similarities between the two groups of epileptics—and their dissimilarity to nonepileptics—were found on memory tests, and since the pattern of the group with symptomatic epilepsy may, by definition of symptomatic epilepsy, be considered a pattern obtained by a group with known brain damage, it is logical to conclude that the defect in function shown by the group with idiopathic epilepsy may be produced by the same circumstances, namely, brain damage or physiological dysfunction of some nature.

Performance on memory tasks contributes directly to intelligence test scores. Therefore, the finding of a definite impairment in performance on memory tasks among epileptics might point to this as being an important factor in the lower mean intelligence scores reported among epileptic patients.

CONCLUSIONS

Both patients with idiopathic and patients with symptomatic epilepsy show somewhat similar impairment in performance on memory and learning tasks. Though there are differences in pattern of impairment between the two groups, each is more like the other than either is like the nonepileptic group.

Both epileptic groups showed the greatest impairment on delayed reproduction of designs.

The group with idiopathic epilepsy differed most from the group with symptomatic epilepsy on reproduction of meaningful material.

Since both new procedures (tactual learning, Procedure V; and complex auditory perceptual task, Procedure VII) differentiated epileptics and nonepileptics, they would appear to be useful and to merit further investigation.

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11. Lennox, W.: The Heredity of Epilepsy as Told by Relatives and Twins, J. A. M. A. **146**:529-536, 1951.

ESSENTIAL PRECAUTIONS IN THE TREATMENT OF NEW PHENOMENA IN MULTIPLE SCLEROSIS

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RECENTLY a procedure was reported by which it is possible to alleviate new or fresh phenomena in multiple sclerosis.[1] In brief, the procedure rests upon the use of vasodilation, but the vasodilation has to be employed in certain specific ways. It cannot be used according to any fixed routine; the type of medication, the dosage, and the frequency of administration often vary with each patient and at different stages in each patient's course. Hence, the procedure is not as simple as one might wish; yet it seems to be effective.

The background and logic, as well as the essential details of the procedure, have been described earlier.[1] Here it is sufficient to mention the belief that the problem of spontaneous remissions has been controlled so far as the evaluation of rapidly acting therapeutic agents is concerned; relief of the fresh phenomena occurs repeatedly and predictably within a few minutes of the vasodilation.

The purpose of this communication is twofold: first, to describe the use of the method in three unreported cases, and, second, to discuss certain variations and precautions necessary in its employment.

The fact that vasodilation would reduce new symptoms has been known for some time.[2] Until recently this fact could not be employed for the long-term benefit of patients.

Mann Fine Chemical, Inc., supplied the histamine phosphate (Mannistamine) used in this project.

This work has been supported by the Fund for Research, Inc., and and the National Multiple Sclerosis Society.

Presidential Address read at a combined meeting of the New York Neurological Society and the New York Academy of Medicine, Section of Neurology and Psychiatry, Nov. 10, 1952.

1. Brickner, R. M.: Management of Acute Episodes in Multiple Sclerosis: Preliminary Report, A. M. A. Arch. Neurol. & Psychiat. **68**:180, 1952.

2. (*a*) Brickner, R. M., and Franklin, C. R.: Visible Retinal Arteriolar Spasm Associated with Multiple Sclerosis: Preliminary Report, Arch. Neurol. & Psychiat. **51**:573, 1944. (*b*) Franklin, C. R., and Brickner, R. M.: Vasospasm Associated with Multiple Sclerosis, ibid. **58**:125, 1947. (*c*) Brickner, R. M.: Significance of Localized Vasoconstrictions in Multiple Sclerosis: Transient, Sudden Miniature Attacks of Multiple Sclerosis, A. Res. Nerv. Ment. Dis., Proc. (1948) **28**:236, 1950. (*d*) Bell, E. Jr.; Williams, G. H., and Karnosh, L. J.: Tetraethylammonium Chloride in Multiple Sclerosis, Cleveland Clin. Quart. **15**:90, 1948. (*e*) Williams, G. H.; Karnosh, L. J., and Tucker, H. J.: Modification of Signs in Multiple Sclerosis Through the Use of Tetraethylammonium Chloride, Neurology **2**:525, 1952. (*f*) Williams, G. H., and Bell, E., Jr: Present Day Status of Multiple Sclerosis, Mississippi Doctor **27**:130, 1949. (*g*) Schmid, E. E.: Personal communication to the author. (*h*) Bell, E., Jr.: Personal communication to the author. (*i*) Bente, D., and Betz, K.: Über eigenartige vegetativ bedingte Phänomene bei der multiplen Sklerose, Arch. Psychiat. **185**:524, 1950.

The duration of relief following a single vasodilation had never been known. It was mistakenly assumed that the duration of improvement was coincident with the duration of the flush, and that 24-hour-a-day vasodilation would be necessary over very long periods for the achievement of any therapeutic benefit. It has now been found that improvement may last several hours, or days, or even longer, after a single flush. With carefully timed repetitions of drug administration, the improvement may be made lasting.

CASES ILLUSTRATING MEANS OF EVALUATING TREATMENT

Not every improvement following vasodilation can be attributed to the flush with assurance. The improvement must occur within a few minutes of the vasodilation; it may occur either during or shortly after the termination of the flush. The sequelae of treatment in the case of B. B. for example, are considered specific results of treatment: With an infusion of histamine phosphate U. S. P. by iontophoresis at 3 p. m., the left heel-to-knee test, which had shown moderate ataxia just prior to this infusion, immediately became normal. There was no further testing until 8 p. m. that evening, when the left heel-to-knee test again showed slight ataxia; immediately after treatment the ataxia disappeared again. At 12:15 a. m. the patient again tested the left heel-to-knee movement, which was found to be ataxic, though less so than at the 8-o'clock observation; again, after an infusion the test showed disappearance of the ataxia. On the patient's awakening the following morning, at 7 o'clock, another testing showed only moderate ataxia, which disappeared immediately after another treatment.

Improvement like that in the case of N. B., however, cannot be definitely attributed to treatment. This patient had had four whiffs of amyl nitrite at 2:30 p. m. and showed no change in the symptoms of his left hand before leaving the office. Inasmuch as he had to leave before the flush was fully over, he himself should have made repeated observations in the immediate future, but he did not. Later, he was unable to make a report regarding the condition of this hand beyond the statement "At 8 p. m. my hand felt better."

PREVIOUSLY UNREPORTED CASES

CASE 1 (A. D.)—Prior to a new attack A. D., a man aged 45, with known multiple sclerosis, had been in very good condition. The sole residuals of his previous attacks were occasional buckling of the right knee; slight numbness of the left foot, varying slightly in degree; slight tingling and numbness in both hands, including the fingers, and slight difficulty in using the right hand in writing and eating.

The phenomena incident to the new attack were unsteadiness of gait and difficulty in lifting the right leg, for five days; an increase in the numbness of the left foot, to the point of constancy, for one week; increased tingling and numbness of both hands, and increased difficulty in using the right hand in writing and eating because of incoordination, for one week; numbness of the left thigh, calf, and buttock, for one week.

New abnormalities detected on examination were severe ataxia of the left leg and impaired vibratory sense in the toes of the right foot. The increases in old symptoms, as just described, were regarded as fresh phenomena.

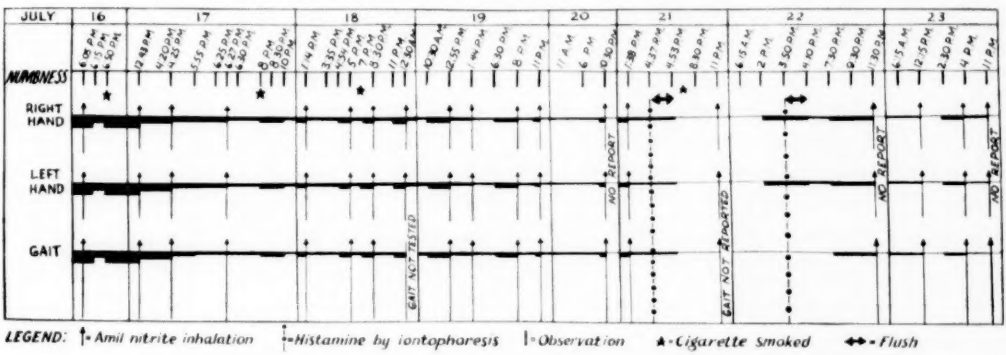
The patient was seen at frequent and regular intervals and received amyl nitrite in doses of three to six whiffs. With each flush, each of the new phenomena showed improvement over the preflush condition (Figure). The symptoms improved simultaneously and also, later, reappeared simultaneously. The periods of improvement became progressively longer, and at the

end of a month of regularly administered flushes the new symptoms failed to return altogether. Treatment was stopped, the patient being in about the same condition as prior to the new attack. The old symptoms were unaffected.

The interpretation of duration of improvement was complicated by the frequent interflush recurrence of tingling in the left buttock and increased numbness in both hands on smoking a cigarette. The symptoms would often wane or disappear again spontaneously after the smoking was stopped. Immediate accentuation of symptoms with smoking has been noted previously.[2b]

It is thought that treatment, and not a spontaneous remission, was responsible for the improvement, because the symptoms disappeared within minutes of the termination of each flush. Repeatedly, when the symptoms returned, they were again abolished within a few minutes of treatment.

CASE 2 (H. R.)—A woman aged 34 was symptom-free after a number of previous attacks of multiple sclerosis, which had been controlled with the vasodilation procedure. On Sept. 10, 1952, she reported a slight tremor of the right arm on brushing her hair. On examination, a mild tremor was noted, but only in the hair-brushing position. A regimen of six whiffs of amyl nitrite every four hours day and night was instituted. With each flush the tremor was reduced to a minimum, although it never reached the zero point.



Diagrammatic representation showing promptness and duration of effects of individual treatments. Only numbness of the hands and gait disturbances are included.

After three days, the medication was reduced to six whiffs of amyl nitrite given as close to every six hours as possible without interfering with sleep; a dose was taken on retiring and arising. The tremor did not always regress between flushes, but when it did, it was regularly reduced to the minimal degree just mentioned. After she had been two and a half weeks on this schedule, the tremor at the hair-brushing position no longer regressed between treatments but remained on a plateau; it was just about discernible.

About three weeks after the onset of this symptom, suddenly, during one of the intervals between flushes, the tremor was noted in the feeding position as well. This was abolished by the next flush; it recurred only a few times and then disappeared altogether; it has remained absent for about four and one-half months, up to the time of writing.

During the course of treatment, the tremor held its improvement for periods of about four hours at first; later, these lengthened to a little more than six hours. Soon the duration of improvement became irregular, lasting from 6 to as long as 12 hours each time. The duration of improvement was, of course, used as the key to timing the doses of vasodilatory drugs.

It was thought that treatment had helped the new symptom markedly but that a permanent residual in one position remained. This situation appeared to resemble closely a type of occurrence reported and discussed earlier,[2b] in which a supposed new scotoma was repeatedly reduced with vasodilation, but not abolished.

CASE 3 (F. A.)—A man aged 49 had had multiple sclerosis for over 20 years. The degree of advancement was still only moderate. His major symptoms were rather marked fatigability; weakness of both lower extremities; moderate imbalance in gait and on his standing erect in a dark room or on entering a dark room; lack of fusion of visual images during fatigue, and numbness and reduction in the strength of both hands.

There had been gradual worsening of all those symptoms for about one and a half years, and there was no way to be certain of the exact duration of the status of any symptom at the time treatment was undertaken. Hence it was unknown to what degree the phenomena which did and did not respond to treatment were really new.

The first inhalation of amyl nitrite, on Sept. 4, 1952, resulted in immediate lessening of numbness in both hands and in improvement in balance, as evidenced by gait and the Romberg tests. Noticeable lessening of staggering in gait continued to occur with each of a series of vasodilations, until a peak was reached by the end of the eighth day. At that time the Romberg test was within normal limits with the eyes open, and the tendency to sway and fall with the eyes closed was much reduced; the heel-to-knee test was within normal limits on both sides, and the gait showed marked improvement in terms of steadiness and lightness. The numbness of the hands was also at a minimum. This plateau, with minor regressions, which were immediately improved by vasodilation, was maintained for the next 10 days, when the patient was discharged to go home with instructions to use histamine by iontophoresis when he deemed it necessary. The latest report and examination on Feb. 13, 1953, showed that the patient was still maintaining the degree of improvement he showed when last seen.

PRECAUTIONS AND VARIATIONS IN TREATMENT

Suddenness of Vasodilation.—Both the size of the dose of the vasodilating drug and its speed of action must be taken into account. Amyl nitrite, for example, acts very swiftly; histamine phosphate administered by iontophoresis affects the blood vessels more gradually. Sometimes the flush has a sudden adverse effect on the symptoms; so far this has always been transient. The impression has been gained that this is most prone to occur when the involvement of the central nervous system is already massive, as a result of earlier attacks. A suddenly induced severe flush is more likely than a gradual, slight one to induce untoward effects.

Sometimes, of course, it is impossible to draw a sharp line between slight and advanced involvement, although the extreme degrees are obvious. The series is too small to warrant the drawing of final conclusions in this respect, but it does appear that even three whiffs of amyl nitrite may be unsafe in a patient with advanced involvement. In patients with severe involvement, even the iontophoretic administration of histamine phosphate must be carried out with great care. The gradually developing flush should be kept at a minimum; a severe flush, even if induced gradually, may produce transient untoward results, when a mild one will not.

A good precaution against transient regression is to have the patient prone throughout the duration of the flush and for a while thereafter.

Amyl nitrite should be tried out in most cases, starting with very mild doses, because it is the drug of choice when it is effective and can be tolerated. Continued observation is needed, because the drug may do no harm at one time but may cause transient regression at others. Histamine phosphate given by iontophoresis has been the next choice. Carbon dioxide is now being tried. Nicotinic acid has proved somewhat undependable in its effects, and doses are therefore very difficult to determine.

Changes in Dosage.—Whatever drug is used, changes in dosage are sometimes indicated. Sometimes the slightest discernible flush will be effective for a while and then, losing its potency, will have to be replaced by a moderate or severe flush; in the same patient a slight flush may be effective again later. It is, of course, wisest to use the smallest dose which can produce maximal improvement, but in the pursuit of these effects one must be bold enough to try large doses if necessary.

CASES ILLUSTRATING TRANSIENT REGRESSION DURING TREATMENT

F. A. (Case 3) was given histamine phosphate by iontophoresis in the same dosage as that used many times before. The flush, however, was much more intense than usual. Twenty-six minutes after the cessation of the infusion, examination showed an increase of the nystagmus and of ataxia of the right upper extremity. These increases were transient.

B. G. had chronic progressive multiple sclerosis. An unsuccessful effort was made to learn whether any help could be given, such as bringing his status back to what it perhaps had been a month before treatment. There were no acute attacks or known new symptoms. Involvement of the central nervous system was massive. The patient stated that on his arising one morning his tremor was "worse during a nicotinic acid flush." Again, several days later, he reported a full flush produced by nicotinic acid, during which, as he stated, "my hands developed a terrific tremor and even my eyes seemed to jump. In addition, I had a severe headache—all of these symptoms disappeared when the flush disappeared." This same patient reported again, two days later, "My gait is worse since taking so much nicotinic acid in the past two days. The regression lasts for a longer period of time after each flush than it did; it returns to the preflush level in about two to three hours, whereas it used to return as soon as the flush ended. I cannot manage my legs or hands as well after the flush as before."

Two months later amyl nitrite was given this patient, with increase in intention tremor within 15 minutes of an inhalation of three whiffs.

G. H., another patient with chronic progressive multiple sclerosis and massive involvement, received nicotinic acid with a resultant full flush rising within eight minutes. The trunkal tremor became so severe that the patient could not stand, and the left leg showed increased tremor in elevation in the prone position.

A. R., another patient with chronic progressive multiple sclerosis and massive involvement, following a flush induced by nicotinic acid had a marked increase in the tremor of the head and left upper extremity. Three days later a smaller dose was given; within one minute an increase in his usually very mild head tremor was noted again. In six minutes the voice became stronger and the speech clearer, however. After 40 minutes, when the flush had almost waned, the increase in head tremor was still evident. Both times, the patient regained his preflush status soon after the flush waned.

B. B., a patient in stationary condition, several weeks after a new attack, and with less total involvement than the other two patients, had responded with noticeable improvement to histamine by iontophoresis but showed a regression after three whiffs of amyl nitrite taken while sitting up. She complained of extreme dizziness, which was relieved only by lying down; her balance became worse immediately after the inhalation, and it did not improve for several hours.

COMMENT

The reasons for these adverse occurrences, especially in the presence of massive damage to the central nervous system, are not known. The surmise seems justified that the neural part of the blood-pressure-regulating mechanism may be disturbed in patients with extensive damage to the central nervous system; the central nervous system may lose a good deal of blood and not regain it fast enough because the normal compensating mechanisms are deficient.

Forbes, Wolff, and Cobb [3] noted paradoxical reaction of blood vessels to histamine infusion in cats. The same thing has been seen in the retinal arterioles of at least one patient with multiple sclerosis treated with other vasodilating drugs.[2b] This may be a factor in the explanation.

With respect to the basis of all the observations, that new phenomena can be lastingly relieved or greatly reduced, no failures have yet been encountered. Some may be anticipated, however. It has already been mentioned [2b] that a constriction might be tight enough or prolonged enough to cause extensive tissue death, either with or without thrombi, such as Putnam [4] described. This would, of course, prevent relief by vasodilation. On the other hand, the amount of actually dead tissue may be very small; it may be surrounded by an area which is still usable but in a state of hypofunction due to vasoconstriction, relievable by vasodilation. This may be presumed to be the explanation of the situation with the scotoma previously described,[2a,c] and referred to above, and of the course of the tremor in the present Case 2.

Real failures may come from a certain type of diagnostic error. If advancement is extensive, a small new lesion may perhaps do no more than add slightly to an existing symptom. A weak leg may merely feel somewhat "heavier." This may not impress the physician, who thus overlooks the occurrence of something which is new and real. Other new lesions may even be silent, and may become old before they combine with one further lesion finally to produce a recognizable symptomatic result. The consequent new incapacity, the combined sequel of lesions old and new, would then not be reversible.

SUMMARY

A procedure for the treatment of new phenomena in multiple sclerosis is outlined in further detail. Certain essential points, including precautions, are emphasized.

Three previously unreported cases of multiple sclerosis are reported, with relief of new phenomena by a therapeutic procedure based on vasodilation. One more patient obtained what appeared to be specific relief, although the duration of the phenomena was uncertain.

3. Forbes, H. S.; Wolff, H. G., and Cobb, S.: Cerebral Circulation: X. Action of Histamine, Am. J. Physiol. **89**:266, 1929.

4. Putnam, T. J.: Evidences of Vascular Occlusion in Multiple Sclerosis and "Encephalomyelitis," Arch. Neurol. & Psychiat. **37**:1298, 1937. Putnam, T. J., and Adler, A.: Vascular Architecture of the Lesions of Multiple Sclerosis, ibid. **38**:1, 1937. Fog, T.: Topographic Distribution of Plaques in Spinal Cord in Multiple Sclerosis, ibid. **63**:382, 1950.

BULBAR RETICULAR FORMATION AND TREMOR

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THE TERM tremor denotes rhythmic alternating movements of a part of the body, such as might result from rhythmic contraction and relaxation of groups of muscles or alternating contraction and relaxation of antagonistic muscles at a joint. Its frequency has been variously described as between 3 and 24 per second.[1] The occurrence of such rhythmic movements in human disease was first described by Parkinson[2] in 1817, and since then it has repeatedly been shown that the pathologic changes associated with paralysis agitans are multiple and usually include the zona compacta of the substantia nigra, the globus pallidus, and the ansa lenticularis. Other regions sometimes involved include the neocortex, caudate nucleus, putamen, nucleus amygdalae, zona incerta, Forel fields H-1 and H-2, thalamus, hypothalamus, zona reticularis of the substantia nigra (Soemmerring's ganglion), corpus subthalamicum, mamillary bodies, and other structures of the midbrain, as well as the pons and medulla.[3]

Attempts to influence these rhythmic movements therapeutically have been limited largely to the use of various drugs, the majority of which are anticholinergic in action, with the exception of amyl nitrite, recently introduced by Garai.[4] The results of surgical therapy are not entirely satisfactory,[5] and it is evident that a

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1. Jung, R.: Physiologische Untersuchungen über den Parkinsontremor und andere Zitterformen beim Menschen, Ztschr. ges. Neurol. u. Psychiat. **173**:*263-332*, 1941.

2. Parkinson, J.: An Essay on the Shaking Palsy, London, Sherwood, Neely & Jones, 1817.

3. (*a*) Davison, C.: Role of the Globus Pallidus and Substantia Nigra in the Production of Rigidity and Tremor: A Clinico-Pathological Study of Paralysis Agitans, A. Res. Nerv. & Ment. Dis., Proc. **21**:*267-333*, 1942. (*b*) Meyers, R.: Modification of Alternating Tremors, Rigidity and Festination by Surgery of the Basal Ganglia, ibid. **21**:*602-665*, 1942.

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more effective approach to this problem could be achieved if more were known about the pathophysiology of tremor.

Attempts to reproduce static tremor experimentally date back to 1902, when Schüller [6] destroyed the caudate nucleus in dogs and Wilson [7] produced unilateral lesions of the lentiform nucleus without producing tremor or involuntary movements. Subsequent attempts to reproduce the resting tremor by lesions of the basal ganglia have also failed (Morgan [8]; Lidell and Phillips [9]; Ranson and Berry [10]; Kennard and Fulton,[11] and Brown [12]).

The first successful attempt to produce tremor experimentally was reported in 1924 by Mella,[13] who intoxicated monkeys with manganese chloride and produced Parkinsonian-like tremor, but the diffuse location of pathologic changes throughout the brain did not allow any anatomical correlation. The production of tremor at rest by discrete lesions has been more difficult. Ward, McCulloch, and Magoun [14] have shown in monkeys that bilateral electrolytic lesions at the base of the tegmentum, extending from the red nucleus to the caudal end of the pons, were followed by a static tremor of 8 per second. The monkeys also showed mask-like facies, sluggish movements, and poverty of emotional expression. These studies have been further elaborated by Peterson, Magoun, McCulloch, and Lindsay,[15] although

falitsche, Schizophrene **5**:117-122, 1936. Putnam, T. J., and Herz, E.: Results of Spinal Pyramidotomy in the Treatment of Parkinsonian Syndrome, Arch. Neurol. & Psychiat. **63**:357-366, 1950. Oliver, L. C.: Surgery in Parkinson's Disease: Complete Section of Lateral Column of Spinal Cord for Tremor, Lancet **1**:847-848, 1950. Delmas-Marsalet, P., and van Bogaert, L.: Sur un cas de myoclonies rhythmiques continues déterminées par une intervention chirurgicale sur le tronc cérébral, Rev. neurol. **64**:728-740, 1935. Bucy, P. C., Editor: Involuntary Movements, in The Precentral Motor Cortex, Ed. 2, Urbana, Ill., University of Illinois Press, 1949, pp. 395-423. Foerster, O. and Gagel, O.: Die Vorderseitenstrangdurchscheidung beim Menschen: Eine klinisch-patho-physiologisch-anatomische Studie, Ztschr. ges. Neurol. u. Psychiat. **138**:1-92, 1932. Horsley, V.: The Linacre Lecture on the Function of the So-Called Motor Area of the Brain, Brit. M. J. **2**:125-132, 1909.

6. Schüller, A.: Reizversuche am Nucleus caudatus des Hundes, Arch. ges. Physiol. **91**:477-508, 1902.

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8. Morgan, L. O.: The Corpus Striatum: Study of Secondary Degeneration Following Lesions in Man and of Symptoms and Acute Degenerations Following Experimental Lesions in Cats, Arch. Neurol. & Pscyhiat. **18**:495-549, 1927.

9. Lidell, E. G. T., and Phillips, C. G.: Experimental Lesions in the Basal Ganglia of the Cat, Brain **63**:264-274, 1940.

10. Ranson, S. W., and Berry, C.: Observations on Monkeys with Bilateral Lesions of the Globus Pallidus, Arch. Neurol. & Psychiat. **46**:504-508, 1941.

11. Kennard, M. A., and Fulton, J. F.: Corticostriatal Interrelation in the Monkey and Chimpanzee, A. Res. Nerv. & Ment. Dis., Proc. **21**:228-245, 1942.

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13. Mella, H.: The Experimental Production of Basal Ganglion Symptomatology in Macacus Rhesus, Arch. Neurol. & Psychiat. **11**:405-417, 1924.

14. Ward, A. A. Jr.; McCulloch, W. S., and Magoun, H. W.: Production of an Alternating Tremor at Rest in Monkeys, J. Neurophysiol. **11**:317-330, 1948.

15. Peterson, E. W.; Magoun, H. W.; McCulloch, W. S., and Lindsay, D. B.: Production of Postural Tremor, J. Neurophysiol. **12**:371-384, 1949.

the relationship to other types of gross tremor not involving the digits is obscure.[16] However, since the site of the destructive lesions cannot be the origin of tremor, additional mechanisms must be involved.

One possible hypothesis is based on the postulate that central denervation hypersensitivity to acetylcholine can occur. If one assumes that these critical lesions in the rostral tegmentum or the lower part of the diencephalon interrupt projections to the critical portions of the bulbar reticular formation, it would follow that these deafferented neurones would then become hypersensitive to acetylcholine. Furthermore, if the normal activity of these bulbar reticular neurons is manifested as rhythmic movement, autonomous excitation by acetylcholine could well evoke the static tremor seen after these lesions.

Certain assumptions on which this hypothesis is based are susceptible to experimental attack. The purpose of the present study is first to determine whether circuits exist within the bulbar reticular formation whose experimental excitation results in rhythmic movements resembling static tremor. If such circuits do exist, the second problem is to study the relation of these movements to Parkinsonian tremor by comparing the action of clinically effective drugs on this induced tremor.

MATERIALS AND METHODS

Eighteen monkeys (Macacus mulattus) were used in these experiments, 7 males and 11 females, the weight of which ranged from 3.0 to 6.2 kg. The animals were lightly anesthetized with diallylbarbituric acid (Dial).[17] The monkeys were then placed in a sterotaxic instrument, and a small trephine hole was made in the skull in 12 monkeys to allow insertion of the stimulating electrode. In three monkeys the skull was widely opened to allow recordings to electrocorticograms. In three additional animals the electrode was implanted by a rigid plastic plug in the skull and stimulation carried out after recovery from inhalation anesthesia.

Stimulations were carried out with a Model 3-C Grass stimulator, sometimes in conjunction with an isolation unit of our construction. Stimulation consisted of 1-msec. biphasic pulses, usually at 60 cps, and of 3 to 5 seconds' duration. The voltage varied from 1 to 10. The deep, stimulating electrode consisted of No. 22 nicochrome (Nichrome) wire insulated except for the sharpened tip. The plane of insertion of the electrode can readily be seen in Figure 1. The numbers used in this sketch of the midsagittal plane are the actual settings of the stereotaxic instrument and are explained in the legend. One can thus ascertain the plane and position of the stimulating electrode by comparing this sketch with the various photomicrographs shown.

Stimulations were carried out along tracts 1 and 3 mm. lateral to the midline. One to four such tracts were made in each animal, stimulation being carried out at 1-mm. intervals along these tracts. After the results of stimulation in the first seven animals were known, the coordinate settings, microscopic location of the tracts, and the production of tremor were correlated with the weight of the head and the body. In all subsequent experiments these correlations were used to correct the coordinate settings, so that uniform anatomical placement of electrodes was achieved.

Recording of tremor was done by attaching the arms or legs of the animal to an electromechanical strain gauge, the output of which was connected to a carrier amplifier and an ink-

16. (*a*) Carrea, R. M. E., and Mettler, F. A.: Physiologic Consequences Following Extensive Removals of the Cerebellar Cortex and Deep Cerebellar Nuclei and Effect of Secondary Cerebral Ablations in the Primate, J. Comp. Neurol. **87**:169-288, 1947. (*b*) Whittier, J. R., and Mettler, F. A.: Studies on the Subthalamus of Rhesus Monkey: II. Hyperkinesia and Other Physiologic Effects of Subthalamic Lesions, with Special Reference to the Subthalamic Nucleus of Luys, ibid. **90**:319-372, 1949.

17. The diallylbarbituric acid (Dial) was furnished by Ciba Pharmaceutical Products, Inc.

recording system equipped with a time marker. Electrocorticograms, electrocardiogram, and respirations (via a thermocouple) were recorded by a conventional eight-channel Grass electroencephalograph.

Sections of all brains for microscopic study were embedded in low viscosity nitrocellulose (L. V. N.), sectioned at a thickness of 30 to 50 μ, and stained with the Weil and Nissl methods.

RESULTS

The effects of stimulation have to be looked upon cautiously, since it should not be forgotten that overpowering stimuli, as compared with physiological activity, were used. Furthermore, the effect of anesthesia on the activity of the reticular formation of the brain stem, a fact noted by Ranson and Magoun,[18] must be recognized.

In all save three experiments, the animal was lightly anesthetized with diallylbarbituric acid. The eyes were closed, and no spontaneous movements were present. The pupils were fairly constricted. Stimulation was usually started at a point designated by the coordinates H + 10. Stimulation then was carried out as the electrode was advanced millimeter by millimeter, with the production of varied and complex responses. With experience, it became possible to predict the general features of the response which would be elicited from different levels of the reticular formation, but the details of the pattern and peripheral distribution of the responses were more variable. Attention was focused primarily on rhythmic responses, and only occasional observations were recorded involving the multitude of other phenomena elicited by stimulation in this region. Thus, no effort was made to analyze the complex eye movements and pupillary changes observed, the details of tonic posture produced, or the respiratory and autonomic responses elicited. Observations regarding the presence and degree of awakening response were made in somewhat greater, but not exhaustive, detail. A condensed, representative protocol of the observations on stimulation along a single tract follows.

TS 27.—Macacus mulattus; 4.4 kg.; Diallylbarbituric acid anesthesia.

Stimulation: 1 msec., 60 a second; biphasic; 10 volts

Coordinates: R 3, A 43, at angle of 29 degrees

H + 5 through H + 1: No response

H — 0: Slight closure of mouth

H — 1 through H — 3: No response

H— 4 through H — 7: Slight awakening response

H — 8: Moderate awakening response; minimal tonic contraction of right shoulder and arm, lower lip, and tail

H — 9: Same as H — 8 plus tonic contraction of right temporal muscle

H — 10: Closure of both fists; minimal "tremor" in left second and third; lowering of both upper lids; flexion of legs on chest; tonic contraction of right shoulder, right temporal muscle, and lower lip

H — 11: "Tremor" of fingers and toes, greater on left side than on right, at about 15 per second, initial narrowing, followed by extreme dilatation of left pupil; right pupil remaining miotic; mild torsion of entire body to the left, similar to the "tegmental reaction"

H — 12: Same as for H — 11, but tremor more marked, with wider excursion; tonic contraction also more marked; both pupils maximally constricted; initial respiratory arrest in inspiration; stimulating current progressively reduced to 3 volts, at which point tremor of chin and lips at 25 per second was only response

18. Ranson, S. W., and Magoun, H. W.: Respiratory and Pupillary Reactions Induced by Electrical Stimulation of the Hypothalamus, Arch. Neurol. & Psychiat. **29**:1179-1193, 1933.

H — 13: Same responses except that tremor of right cheek, chin, and lower lip was present at 10 volts; tremor in fingers of left hand and both legs also present; increase in tremor with stimulatory current reduced to 6 volts; reduction in amplitude of tremor with further reduction to 4 volts

H — 14: Same general pattern as with H — 13; minimal tremor alone present at 4 volts

H — 15: Same general pattern of tremor; excellent tremor of fingers of left hand, consisting of alternate flexion and extension of all fingers, with greatest extension in distal phalanx of thumb; frequency about 12 per second.

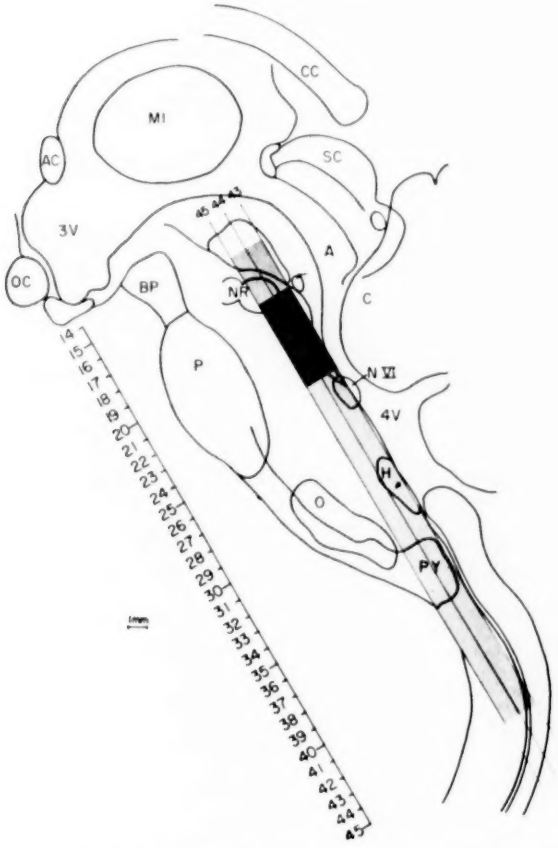

Fig. 1.—Sagittal view of brain stem of the monkey, showing composite of points stimulated which produced tremor. The tremor was marked after stimulation of the densely hatched area.

H — 16: Tremor confined to upper and lower lips; only tonic movements of extremities; both pupils dilated and right eye converged; salivation; respiratory arrest; only tonic movements obtained at 6 volts

H — 17: Tremor of right ear, chin, and lower lip

H — 18: Marked tremor of chin, right side of face, and right leg; urination; salivation; respiratory arrest

H — 19: Tonic movements only at 10 volts

H — 20: All subsequent stimuli to be at maximum of 6 volts; little tremor of face; urination; tremor of face increased when stimulating current reduced to 5 volts

H — 21: Tremor of platysma muscles, ears; tonic contraction of face; excellent tremor of face with 4 volts

H — 22: Tremor of proximal part of leg; good tremor of ears, face, platysma, and all extremities on reduction to 4 volts

H — 23: Moderate tremor of forehead, face, platysma, and both legs at 2 volts

H — 24: Some tremor of right side of face and right leg at 2 volts; poor amplitude and not as regular in alternation; more superimposed tonic component

H — 25: Minimal tremor of tail and right leg with tonic component

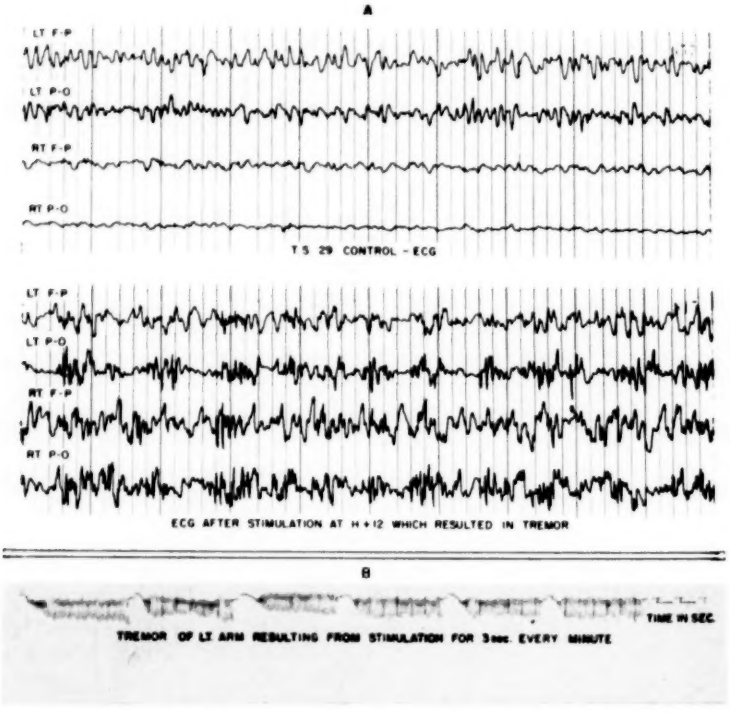

Fig. 2.—*A*, electrocorticogram before and 30 seconds after stimulation of bulbar reticular formation. *B*, strain-gauge myogram of tremor elicited by stimulation of same point in brain stem.

The "awakening response" of Ranson and Magoun [18] or the "sympathetic discharge" of Kabat, Anson, Magoun, and Ranson [19] was always seen; it consisted of slow opening of the eyes with slight to moderate enlargement of the pupils. It was usually accompanied with salivation and chewing or licking movements. In these experiments, this response was first seen with stimulation at about H —4 (Fig. 1)

19. Kabat, H.; Anson, B. J.; Magoun, H. W., and Ranson, S. W.: Stimulation of the Hypothalamus with Special Reference to Its Effect on Gastro-Intestinal Motility, Am. J. Physiol. **112**:214-226, 1935.

and was present in some degree on stimulation down to H —31. Stimulations eliciting the awakening response at rostral levels also resulted in marked activation of the electrocorticogram, as seen in Figure 2*A*. With each consecutive stimulation this activation became more marked; but since this effect persisted for at least 30 minutes, whereas stimulations were carried out every five minutes, this electroencephalographic arousal response was not studied in detail.

TREMOR

Minimal tremor was first seen at coordinates H —8 to H —10 (Fig. 1), and at H —14 the excursion was of sufficient degree to allow satisfactory myographic recording. Maximal tremor was observed between H —18 and H —23, while tremor of decreasing degree could be recorded down to H —44, although the region caudal to H —46 was not explored. Thus, the region from which arousal (electroencephalographic activation) and clinical awakening could be elicited did not coincide with that from which tremor is produced, though the two areas overlapped to a large degree. The tremor elicited from any given locus was always of uniform amplitude and frequency, as seen in Figure 2*B*. The induced rhythmic, alternating movements, which are analogous to the static tremor seen in paralysis agitans, may involve any portion of the animal's body and may take different patterns. They were usually more pronounced on the contralateral side of the body, although homolateral responses were seen. Stimulation at more rostral levels usually evoked a rhythmic tremor, limited to the face, neck, and, occasionally, the fingers. The tremor of the face included fast, rhythmic, up-and-down movements of the eyelids, alternating contraction and relaxation of facial and chewing muscles, alternating protrusion and retraction of the tongue, rhythmic wiggling of the ears, up-and-down movements of the brows, and rhythmic contractions of the platysma muscles. At more caudal levels, all parts of the body took part in the tremor at one time or another, and these movements consisted of alternating shrugging of the shoulders, and alternating contraction of the flexors and extensors of any joint; the amplitude of such movements seemed to be small at proximal joints and much greater at distal joints. The frequency of these rhythmic movements, or tremor, varied from 15 to 25 per second, slower frequencies being observed only occasionally. The frequency of the stimulating current was never lower than 60 per second. Under certain circumstances, such clonic, rhythmic movements were accompanied with a smaller or larger amount of tonic contraction, which occasionally overshadowed the rhythmic response; this was particularly true when strong stimulation was used. The movements elicited by electrical stimulation of the bulbar reticular formation thus represent only crude approximations of the static tremor seen in paralysis agitans, although a pill-rolling rhythmic movement was occasionally evoked which appeared to be identical with the pill-rolling tremor occasionally seen after chronic lesions of the brain stem in the monkey.

The anatomical region from which such tremor-like movements can be elicited is seen in Figure 1, which is a composite of all points in the reticular formation from which tremor was evoked by stimulation. It is seen that the maximum representation for such responses lies in the medial reticular formation between the red nucleus and the nucleus of the abducens nerve. The plane of insertion of the electrode into the brain stem is demonstrated in Figure 3. Since it is difficult to orientate oneself in

this plane, such a section is accompanied by two cross sections of the same specimen, in Figure 4. Here, the rostral cross section is taken at H —13, and the caudal one at H —32, and the longitudinal section covers the area between these coordinates.

Stimulation between the coordinates H —10 and H —46 were carried out on a total of 657 occasions, resulting in the production of tremor in 314 instances. All the productive points lay inside the stippled region noted in Figure 1. In the plane of electrode insertion noted, exploration was carried laterally only 3 mm. from the midline. The anteroposterior extent of the region yielding tremor was not completely mapped, as an area only 2 mm. wide was thoroughly explored, although random observations anterior to this plane extended into the pons. The rostral and caudal limits of the response were satisfactorily secured and are summarized in Figure 1.

Fig. 3.—Histological section (Weil stain) of brain stem in plane of electrode tract.

On three occasions, no or minimal tremor was obtained throughout the extent of the electrode insertion. However forceful, rhythmic vocalization was evoked between coordinates H —12 and H —15. Since this was accompanied by the awakening response, a rather dramatic picture was produced, in which the monkey would open its eyes and bark rhythmically during the stimulation. On histological section, the site of stimulation in these instances was found to be in the tectum in the vicinity of the point marked *X* in Figure 4*A*. The rhythmic vocalization had a frequency of 3 to 5 per second. Both the frequency and the pitch of the vocalization decreased as the electrode was moved caudally.

Bilateral pedunculotomy was carried out prior to brain stem stimulation in four of the initial experiments. The rhythmic responses in these animals were elicited with some difficulty. Moderately good tremor was obtained in one instance, and at autopsy the pedunculotomy was shown to be incomplete. For that reason,

this procedure was abandoned. Electrical stimulation of the reticular formation was carried out in 15 monkeys anesthetized with diallylbarbituric acid. In three other monkeys stimulation of fixed points within the brain stem was carried out

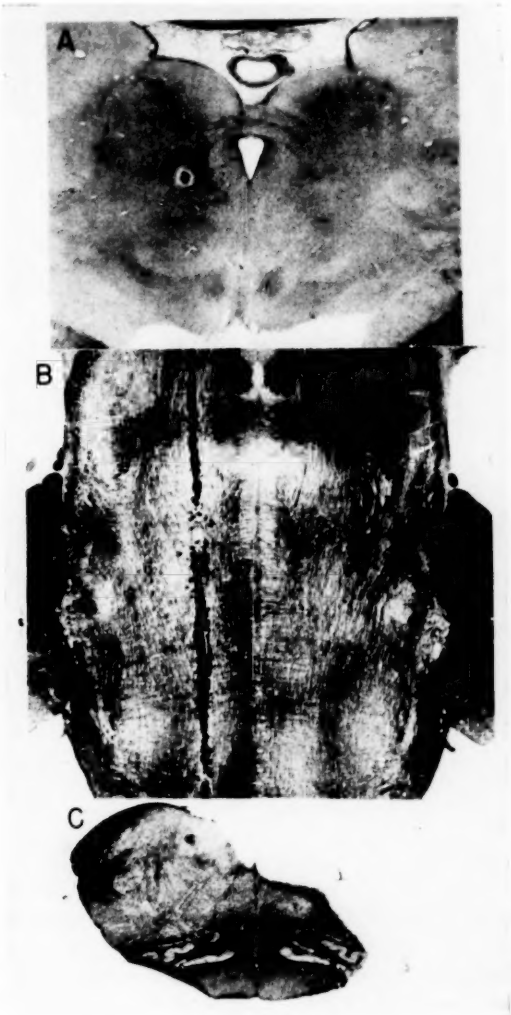

Fig. 4.—*A*, cross section of brain stem at H — 13, at rostral end of block B. The *x* indicates point producing vocalization. *B*, axial section of brain stem in plane of electrode insertion between levels *A* and *C*. *C*, cross section at H — *32* taken at caudal end of block B.

by the use of chronically implanted electrode. The responses obtained in these unanesthetized preparations were identical with those obtained in animals under sedation. However, the threshold in the animal when awake was only one-third to one-fourth that of stimulation in the same location in the narcotized animal.

EFFECT OF DRUGS

If this tremor-like evoked movement is analogous to the static tremor of paralysis agitans, it might be reduced or abolished by the same drugs that are effective clinically. The excellent and constant reproducibility of the evoked tremor (Fig. *2B*) lends itself admirably to this type of study.

In Figure 5 the effect of diethazine hydrochloride (Diparcol) on the induced tremor is seen. This substance is an anticholinergic drug currently in use in the clinical treatment of Parkinsonism. As seen in Figure 5, the amplitude of the

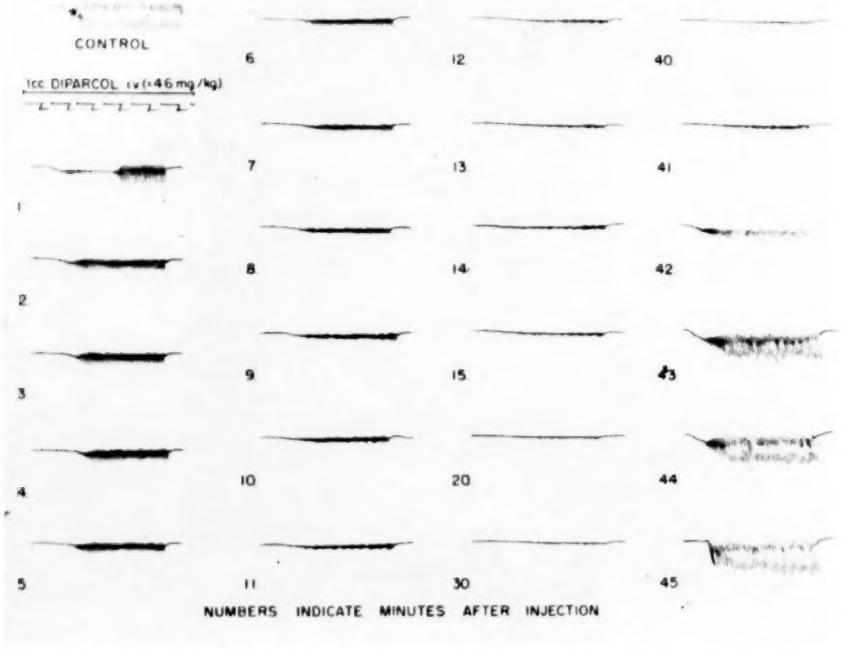

Fig. 5.—Effect of diethazine hydrochloride (Diparcol) on strain-gauge myogram of induced tremor. Numbers indicate minutes after injection.

evoked tremor gradually diminishes after a single intravenous injection of the drug until the tremor disappears, 15 minutes later. It is completely suppressed for 25 minutes, when it returns rather suddenly, over a five minute interval, to the pre-injection amplitude. Inhalation of amyl nitrite causes a partial suppression of the tremor, as noted in Figure *6I*. In Figure *6II* it is seen that scopolamine suppresses the induced tremor almost immediately, the suppression being maintained for over three hours. Scopolamine was the most effective agent in blocking the tremor of all drugs tested. The relatively minimal effect of atropine is seen in Figure *6III*. With the exception of amyl nitrite, all these drugs are anticholinergic in action. Both diethazine hydrochloride and scopolamine are known to be effective in the treatment of Parkinsonism, and amyl nitrite also has a marked, though

transient, effect in human cases, whereas atropine has a poor clinical response. Thus, the induced tremor in the animal is influenced by drugs in the same manner as is Parkinsonism in man.

This being the case, the effect of a group of synthetic anticholinergic compounds [20] on the evoked tremor was studied. Of 10 drugs thus studied, 3 definitely reduced the tremor, 2 others had a minimal effect, while the rest did not influence the evoked tremor at all. The most effective drug was SC-2538 (10-[2-diethylaminopropyl]-phenothiazine methochloride), which was more than 50% as effective as scopolamine. SC-1822 (10-[2-diethylaminoethyl]-phenothiazine methochloride), a closely related drug in chemical structure, was about one-third as effective as scopolamine. Propantheline (SC-3171; Pro-Banthine) was slightly less effective, and SC-3192

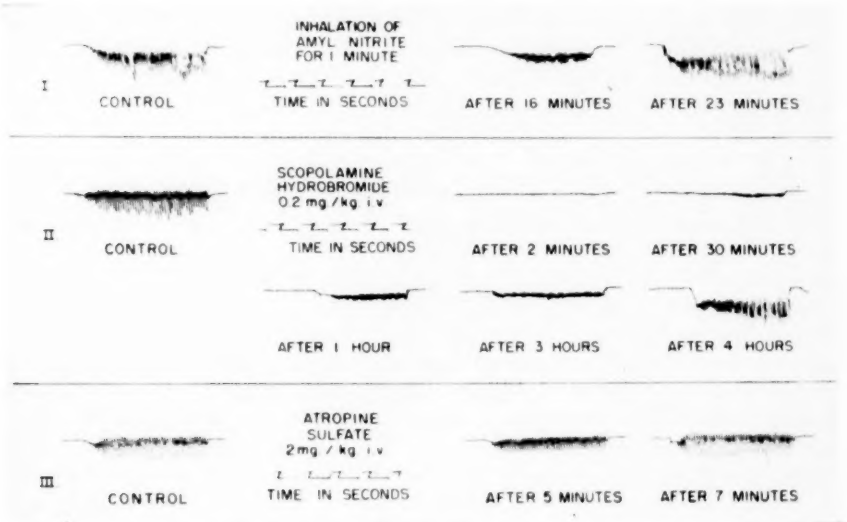

Fig. 6.—*I*, effect of amyl nitrite on strain-gauge myogram of induced tremor: *II*, effect of scopolamine on tremor; *III*, minimal effect of atropine on induced tremor.

(a tertiary compound) was only very minimally effective, in reducing the induced tremor. SC-1876 (10-[2-diethylaminopropyl]-phenothiazine methochloride) had a variable, minimal effect which was somewhat surprising in view of the close chemical relationship between this compound and SC-2538, which was the most effective of the synthetic drugs studied.

The rest of the synthetic compounds were completely ineffective in reducing the tremor. These included SC-3054 (N-phenyl-N-benzyl-β-diisopropylaminoethyl carbamate hydrochloride); SC-3137 (β-diethylaminoethyl xanthene-9-carboxylate ethobromide); SC-3062 (N-phenyl-N-benzyl-β-isopropylaminoethyl carbamate methoiodide); SC-2240 (2-trichloromethyl-1, 3-dioxolane-4-carbinol acid succinate); and methantheline (SC-2910; Banthine; β-diethylaminoethyl xanthene-9-carboxylate methobromide).

20. These compounds and the pharmacological data were furnished through the kindness of Dr. I. C. Winter, G. D. Searle & Co.

The most effective synthetic drugs were all quaternary ammonium compounds, although one tertiary compound was minimally effective. However, three of the ineffective drugs were also quaternary compounds; one was a tertiary compound, and the other a glycerol derivative. There was no apparent relationship between this effect on the bulbar reticular formation and such pharmacological data as the antiacetylcholine effect on isolated ileum, the antibarium action on excised intestine, sympathetic ganglion blockade, or antihistamine activity (Loew spray). However, the three compounds which were most effective against the histamine spasm produced in excised intestine (as measured against diphenhydramine) were also effective against the induced tremor, although the least effective drug in this regard (SC-2538) was the most effective in suppressing the induced tremor.

In summary, the following is a list of all drugs tested in the order of their greatest effect on the induced tremor: scopolamine, diethazine hydrochloride (Diparcol), amyl nitrite, SC-2538, SC-1822, atropine, propantheline (SC-3171), and SC-3192. Thus, scopolamine had the greatest effect, while SC-3192 had minimal or no effect on this particular activity in the reticular formation.

COMMENT

A number of investigators have electrically stimulated the exposed cut surface of the mesencephalon and reported a "tegmental response," but the results of discrete stimulation in this region were first carried out by Ingram, Ranson, Hannett, Zeiss, and Terwilliger,[21] using needle electrodes accurately placed in the brain of anesthetized cats by the Horsley-Clarke technique. Their investigation of the "tegmental reaction" showed that it can be elicited anywhere in the reticular formation caudal to the red nucleus, and it was also seen throughout this extent in the present experiments. As an incidental finding, Ingram and others [21] mentioned that they observed rhythmic movements or tremor when stimulating the subthalamic nucleus and the reticular formation close to the rubrospinal tract in the trapezoid body. This region would largely fall within the hatched area illustrated in Figure 1. The observation by Kabat and associates [19] that tremor may also be evoked by stimulation of the lateral edge of the basis pedunculi, the lateral hypothalamic nuclei, and the subthalamic nuclei has not been entirely confirmed by the present study. Complex repetitive movements following stimulation of the caudate nucleus, putamen, pallidum, nucleus amygdalae, ventral thalamus, or subthalamus and their interconnections have been described by Sweet, McCulloch, and Snider [22] in monkeys after bilateral transection of the cerebral peduncles. They also felt that some somatotopic localization existed in these anatomical structures. The type of movement they describe is apparently not the same as that seen in the present experiments, a difference which may account for the fact that stimulation of basal ganglia and midline structures traversed by these electrode tracts failed to yield the alternating rhythmic response which is analogous to static tremor. These tremor responses were not enhanced after section of the peduncles and were, in fact, decreased or abolished.

21. Ingram, W. R.; Ranson, S. W.; Hannett, F. I.; Zeiss, F. R., and Terwilliger, E. H.: Results of Stimulation of the Tegmentum with the Horsley-Clarke Stereotaxic Apparatus, Arch. Neurol. & Psychiat. **28**:513-541, 1932.

22. Sweet, W. H.; McCulloch, W. S., and Snider, R. S.: Repetitive Movements on Basal Ganglia Stimulation After Transection of Cerebral Peduncles, Fed. Proc. **6**:213, 1947.

Thus, there appear to be neurones embedded in the diffuse matrix of the bulbar reticular formation activation of which produces rhythmic peripheral motor responses analogous to the spontaneous static tremor seen in monkeys and man. Since this evoked tremor may be the only peripheral motor response in the extremities, presumably the cells stimulated are separate from those whose stimulation yields the tonic responses repeatedly seen in the past. However, the relationship of these circuits to clinical awakening and to electroencephalographic arousal is not clear. Insufficient data are available to determine the role these neurones play in the normal integrated activity of the central nervous system and in its normal motor performance. Ingram and associates [21] postulated that the tegmental reaction evoked by stimulation of the reticular formation represents a phylogenetically old motor pattern, which is normally not seen in its isolated form in postnatal life, and this concept is supported by the observation of Windle and Griffin [23] that the earliest movements that can be observed in kitten embryos are bending of the neck and tonic postures analogous to the tegmental responses elicited by tegmental stimulation. In a similar fashion, Jung [1] has postulated that tremor represents a phylogenetically early form of movement (cf. movements of fins of fishes), which is depressed by the elaborate development of the nervous system in higher forms. He goes on to postulate that lesions which block these inhibiting higher influences thereby release the phylogenetically old pattern of rhythmic movements and clinical tremor appears.

We have postulated that the lesions producing Parkinson-like tremor interrupt fibers terminating on those cells in the bulbar reticular formation experimental activation of which yields rhythmic tremor. These deafferented neurones then become hypersensitive to acetylcholine, the source of the acetylcholine being the nearby uninvolved cells of the reticular formation in which these particular cells are embedded. In this regard, it may be that the reticular formation, with its multiplicity of functional systems which are partially intermeshed anatomically, may represent optimal conditions for the manifestation of central denervation hypersensitivity to acetylcholine. One must further assume that the responsible lesion interrupts those projections to cells yielding rhythmic tremor and does not involve projections to other cells, of different function, in the same portion of the brain stem. It is conceivable that emotional tension in the human may be associated with increased activity in these neighboring circuits, resulting in increased liberation of acetylcholine and accentuation of tremor, as is commonly observed. That a slowly developing mechanism, such as denervation hypersensitivity to acetylcholine, is operative both in experimental Parkinsonism in monkey and in the disease in man is indicated by the fact that the tremor does not appear for some time after the production of the lesion (days or weeks in the monkey; weeks, months, or possibly years in man).

It may even be that these particular systems are peculiarly dependent on acetylcholine mechanisms. The fact that suitable anticholinergic drugs will differentially reduce or abolish the peripheral rhythmic motor response without alteration of threshold of the motor cortex or alteration of accompanying tonic responses might lend support to this hypothesis. Since the technic of electrical stimulation, even with stimulating voltages of less than 1, must produce an overwhelming activation

23. Windle, W. F., and Griffin, A. M.: Observations on Embryonic and Fetal Movements of the Cat, J. Comp. Neurol. **52**:149, 1931.

of these systems as compared with normal physiological activity, it is somewhat surprising that suitable anticholinergic drugs can have so profound an effect. The relationship of these findings to clinical Parkinsonism is further suggested by the fact that those drugs which are most effective against clinical tremor are also the ones which are most effective in reducing or abolishing the electrically induced tremor. In addition to the possible conclusions which may be drawn regarding the mechanism of tremor, this method represents a rapid means of screening drugs for their possible usefulness in human Parkinsonism. It was so used in these experiments, but, unfortunately, the series of synthetic drugs tested did not yield any compounds whose potentialities even equal those already available for clinical use. However, the method is now available, and it is hoped that others may be more fortunate.

Clinical Parkinsonism represents a complex of peripheral manifestations, of which tremor is only one. The experimental findings reported have possible bearing only on the static tremor. The region of the reticular formation from which this tremor may be elicited extends rostrally to the level of the red nuclei. Lesions of the reticular formation in the monkey at the level of the red nuclei produce chronic tremor similar to that seen in man.[14] The distribution of neurones in man whose activation will yield rhythmic movement is not known, and it is thus possible that they may extend to more rostral levels than in the monkey. Unfortunately, discrete, localized lesions producing tremor in man are most unusual, and anatomical evidence comparable to that available on the experimental animal is not yet available. It may also be fortuitous that those drugs which are effective in the treatment of Parkinsonism are also anticholinergic in action and thus that central denervation hypersensitivity to acetylcholine does not play a major role. At the present time, however, the proposed mechanism represents at least an interesting, if unproved, hypothesis.

SUMMARY AND CONCLUSIONS

High-frequency electrical stimulation of the medial reticular formation of the brain stem in monkeys produced a rhythmically alternating peripheral movement analogous to tremor. This could be elicited from the entire extent of the medial reticular formation, from a level just rostral to the nucleus ruber caudally to the pyramidal decussation.

This evoked tremor may be differentially reduced or abolished by parenteral administration of anticholinergic drugs, the most effective drugs being those which have been demonstrated to be clinically useful. Of 10 new synthetic drugs tested, none was as effective as scopolamine or diethazine hydrochloride (Diparcol) in suppressing this evoked tremor.

The hypothesis is advanced that the lesions in the rostral tegmentum or lower diencephalon which produce tremor such as that seen in Parkinsonism interrupt projections to these neurones in the medial reticular formation. These deafferented cells subsequently become hypersensitive to acetylcholine. Activation by locally liberated acetylcholine then yields the observed tremor. For this reason, suitable anticholinergic drugs reduce the tremor in Parkinsonism.

ROLE OF "BODY IMAGE CONCEPT" IN PATTERN OF IPSILATERAL CLINICAL EXTINCTION

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THE THEORETICAL basis for the empirically derived pattern of rostral, or face, dominance which is elicited by multiple simultaneous cutaneous stimuli has not yet been established. Several theories have been proposed; none has been completely satisfactory. The major physiological modes of action advanced have been cortical suppression,[1] as activated by "specific" areas, and the direct interaction of the first and second cutaneous sensory systems.[2] Even if it is allowed that suppression is an experimentally proved physiological phenomenon, the time required for effective suppression, as established in animal studies, is incommensurately long compared with clinical extinction. The sensory interaction theory appears plausible, but it has not yet been experimentally shown to be operative either in multiple ipsilateral or in simultaneous bilateral stimulation.

Psychologically, "inattention," organismic, and gestalt theories have been formulated to account for the observed phenomenon of extinction. These formulations appear too descriptive and too general to be effective explanations for clinical extinction processes. Further inadequacies of these theories have been discussed in some detail by Bender.[1]

Denny-Brown and his associates [3] have evolved a psychophysiological explanation for some elements of the observed extinction phenomena. They postulate, as did Goldstein [4] and Bender,[1] that there is a fundamental disturbance in primary perception when there is failure to resolve multiple stimuli applied to the body surfaces. Denny-Brown and associates term this general phenomenon "amorphosynthesis" and propose that this is a primary behavioral process. They present clinical data to show that the "body schema," in the Schilder sense,[5] is not involved as a primary process in extinction.

From the United States Naval Hospital.

1. Bender, M. B.: Disorders in Perception, with Particular Reference to the Phenomena of Extinction and Displacement, Springfield, Ill., Charles C Thomas, Publisher, 1952, p. 109.

2. Cohn, R.: On Certain Aspects of the Sensory Organization of the Human Brain: A Study in Rostral Dominance as Determined by Ipsilateral Simultaneous Stimulation, J. Nerv. & Ment. Dis. **113**:471-484, 1951.

3. Denny-Brown, D. E.; Meyer, J. S., and Horenstein, S.: Significance of Perceptual Rivalry Resulting from Parietal Lesions, Brain **75**:433-471, 1952.

4. Goldstein, K.: The Organism: A Holistic Approach to Biology Derived from Pathological Data in Man, New York, American Book Company, 1939.

5. Schilder, P.: Mind: Perception and Thought in Their Constructive Aspects, New York, Columbia University Press, 1942.

It is the purpose of the present communication to present material indicating that the pattern of ipsilateral extinction (rostral dominance) is the result of an elemental disturbance in the "body image concept."

In the phenomenon of clinical extinction it has been repeatedly observed that normal children between the ages of approximately 3 and 6 years present a reasonably uniform and repeatable pattern of extinction when paired stimuli are applied simultaneously over the face and hand, the shoulder and hand, the hip and ankle, and so on. In my experience [6] it has been the predominant pattern that the face dominates all caudal stimuli, the shoulder obliterates all distally applied stimuli over the

Fig. 1.—Commonest type of drawing. Solid circles indicate complete rostral dominance; half-solid circles, transient rostral dominance.

upper extremites, and the hip extinguishes all simultaneously applied stimuli to distal points on the lower extremities. Stimuli applied to the hip and to elements of the upper extremity, including the shoulder, result in nonrecognition of the stimulus to the upper extremity, but the hand tends to dominate the knee and ankle regions. These interextremity dominances, however, are less precise and less capable of repetitious elicitation than are the intraextremity and head phenomena. In my material no clear uniformity of pattern was elicited in torso-versus-extremity testing.

6. Cohn, R.: On Certain Aspects of the Sensory Organization of the Human Brain: II. A Study of Rostral Dominance in Children, Neurology **1**:119-122, 1951.

As is well known, the general pattern of extinction observed in children duplicates to a high degree that which is observed in the adult in states of dissolution of normal brain function, as a result of structural lesions of the brain, primarily in the post-Rolandic regions.

That the patterns of extinction described above are closely related to the body image concept in the child, and to the dissolution of this formulation in the adult, is derived from a study of drawings of the human figure executed by children with normal and abnormal brain function and by adults with evident pathological lesions of the brain.

In the study of approximately 200 consecutive children, especially those between 3½ and 5 years of age, who, as part of the clinical neurological examination, were

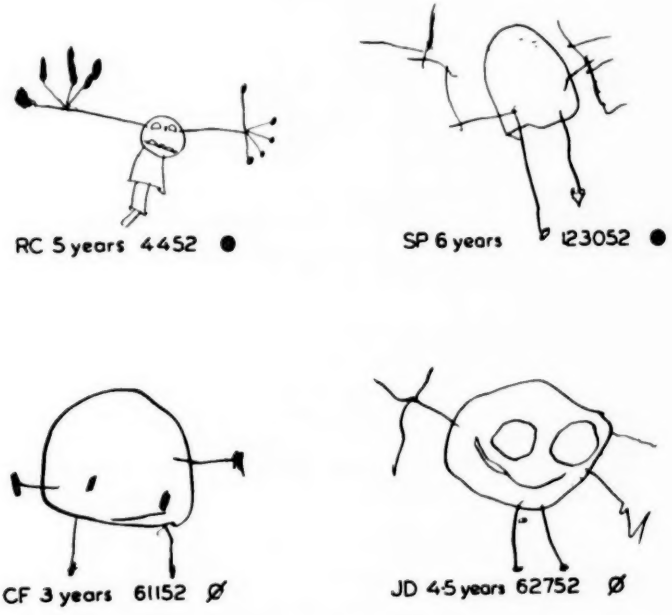

Fig. 2.—Less frequent types of drawings. Solid circles indicate complete rostral dominance; circles with diagonal indicate rostral dominance could not be elicited.

asked to draw the picture of a boy or a girl, it was observed that a characteristic picture emerged. The most usual delineation (Fig. 1) consisted of a roughly circular head with smaller inscribed circles symbolizing the eyes and nose. The mouth was sometimes absent; at other times it was drawn with varying degrees of complexity. Horizontal lines of variable length which abutted the head symbol were designated as upper extremities (frequently these lines were absent); distal anatomical elements, such as fingers, were usually absent, or very simple in design. A pair of vertical lines were attached to the lower or lateral portions of the "head" for the lower extremities; in general, the latter lines were longer and more prominent than those representing the upper limbs. In all these pictures the head was by far the most prominent, and the most central component, of the figure.

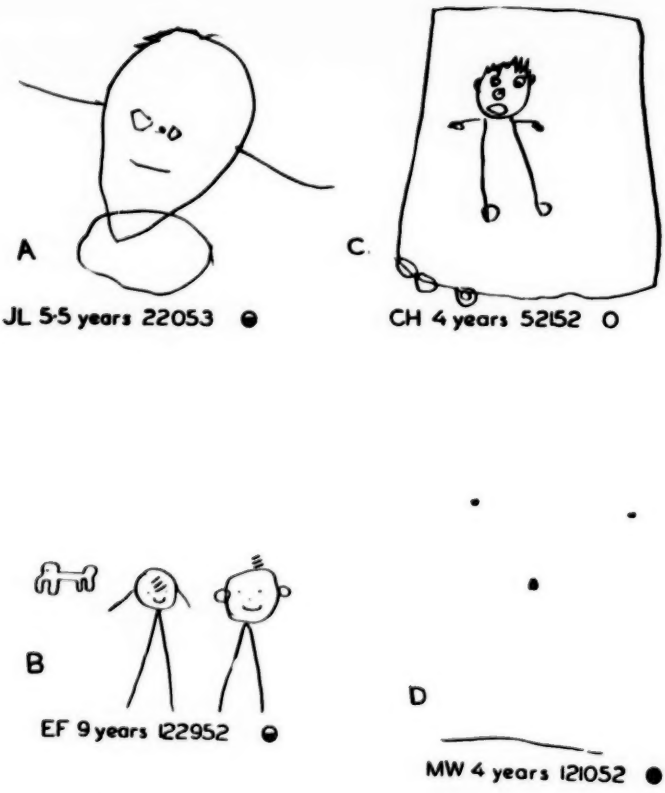

Fig. 3.—Unusual drawings. *A* and *B* are drawings by retarded children; *C*, a drawing by a precocious child; a unique picture. Solid circles indicate complete rostral dominance; half-solid circles, transient rostral dominance; clear circles, resolution of all multiple simultaneous stimuli.

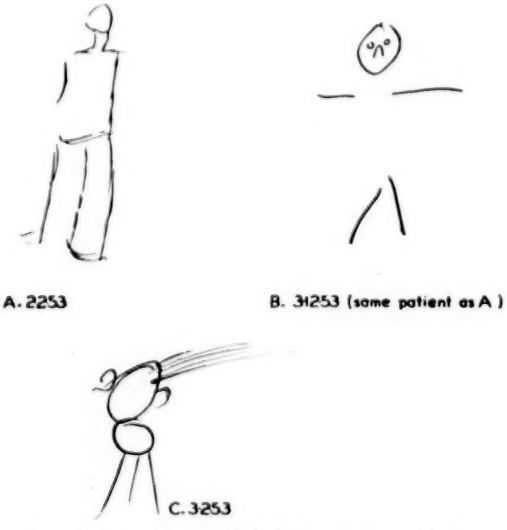

Fig. 4.—Drawings of brain-injured adult subjects.

In a smaller number of cases the same general configuration as that described above was illustrated; but, in addition, hand elements were shown; these formed a relatively prominent part of the picture (Fig. 2). In Figure 3 several unique patterns are presented. *A* and *B* are pictures obtained from clinically "retarded" children; *C* represents the output of a precocious child; in *D* the child utilized the edges of the paper as the boundary for the head and placed facial features as noted. The presented pictures were in no way connected with disturbances in executive mechanisms, since all the children were able to draw lines, circles, and acute angles.

The major fact that emerged from all these pictures was that the head formed the central theme of all the body-image compositions. Thus, there was pictorial rostral dominance. These types of pictures were sufficiently constant that they are believed to represent the primary body image concept of the child.

In certain adults with brain damage who were also asked to draw the human figure it was observed that the depictions were grossly malformed or were very simple in form (Fig. 4). The malformations, or incompletions, were usually in the hemianopic, or "hemi-inattention" side. In previous work it was assumed that the amputations of the depicted figures were the direct result of visual extinction, or the result of true hemiblindness in the involved field. But this assumption was necessarily modified when it was recognized that some patients failed to complete the drawings even when their pictures were placed upright in the intact visual field and they were asked whether the picture looked proper to them; the failure persisted even when the picture was inverted so that the incomplete parts were in the intact field of vision. These observations might not be decisive, except that the same people would be able to resolve and name two moderate-sized, nonrelated objects when these objects were placed in the same visual field. Transiently, moreover, these patients showed disturbances in topognostic functions. Often, when they were asked to raise the right hand, the left would be elevated. Denny-Brown and associates [3] noted the same phenomenon. However, they assumed that the right side of the brain, even of right-handed persons, was sometimes dominant for topognostic function. This appears to be an ad hoc assumption. In this connection, the recognition and naming of body parts of a manikin or the body parts of the examinner do not constitute a critical test of topognostic function. This is because these tests categorize, and consequently act as paradigms, or cues, for the body parts in a way similar to that in which approximate sounds or rhythms assist the "amnestic-dysphasic" patient to recall names of objects.

COMMENT

The spontaneity and universality [7] of the presented type of drawings by children appear to validate the major premise of the proposition that there is a gross equivalence between the pictorial representation and the body image concept of the subject. It is important to note, however, that in some of the children who showed such drawings, with the head as the largest and most prominent part, as observed in the figures, no persistent rostral dominance could be elicited by simultaneous sensory stimulation. These data make it clear that there is a differential maturation of the executive and conceptual operations, with the pictorial ability lagging behind the ability to resolve simultaneously applied ipsilateral cutaneous stimuli.

7. Goodenough, F. L.: Measurement of Intelligence by Drawings, Chicago, World Book Company, 1926.

Two normal children of this entire series showed proper anatomical relationships of the head, torso, and extremities in their drawings; nevertheless, strong rostral dominance was elicited on sensory testing. Despite these exceptions, the overwhelming generality was that anatomically adequate pictures were associated with resolution of multiple ipsilateral stimuli. This ability to resolve repeatedly two or three stimuli generally occurred at about the 6 year level.

Some older children in states of intoxication, either as the result of postictal activity or for other dysmetabolic causes, were able to execute reasonably correct anatomical drawings but were unable adequately to resolve widely dispersed multiple simultaneous cutaneous stimuli. The explanation of this discrepancy appeared to be not only that the toxic subject was allowed sufficient time to recreate his body image concept in the drawing, but that, with each line accomplished in the pictorial display, visual associations were reactivated and reinforced, so that the complete figure developed into a reasonably correct anatomical configuration. Contrary to these slow, visually controlled, and reinforced executive operations, the relatively "unimodal" multiple cutaneous stimuli required alert, immediate perception in order that proper resolution might be accomplished. This immediacy demanded a high level of sentiency, and this high level of sentiency was precisely what the toxic brain could not achieve. Consequently, there was the return to a simpler pattern of body image concept, as determined by the extinction of the distal stimulus.

In this presentation it is hypothesized that there are at least three levels of action in the achievement of the highly organized body image concept. The first assumption is that the physiological end-organs transduce a pattern of electric discharge that is appropriate for the gross body segment stimulated. This operates in a specific space-time reference. This physiological segmental pattern superimposes on, and interacts with (modulates), the past experiential background activity to generate a psychological "perception." Perception may, consequently, be considered, in this idealized action, as a phenomenon of a single sensory mode. This constitutes the second basic assumption. However, whether any percept can be departmentalized into a single modality might well be disputed, since the sentient organized being, except under the most artificial conditions, perceives not only isolated single-class stimuli but stimuli outside the major class. This physiological and psychological diffusion occurs even with the artificial conditions established during testing for pinprick perception in a clinical neurological examination. Along with the mechanical pinprick, not only is the patient forcibly made to attend to stimuli belonging to the class of pinprick but his feelings of stoicism, his past experience with pinpricks, the presence of various observers, and their possible attitudes must activate widely dispersed integration mechanisms. Along with this, the patient is bombarded by complex sounds and cues of touch, temperature, and other qualities of the test stimulus used. Thus, the aforementioned "unimodality" assumption is necessarily used in the functional sense of a major figure operating in a universal background.

The third assumption of this communication is that a concept is the direct result of the hierarchal organization and correlation of percepts of the several individual responsive modalities. The concept, consequently, differs from the percept only by the complexity of the organization. In this sense, the percept is the "something" happening; the concept is the "what" happening.

With the model capable of being derived from the above postulates, it is clear that the organism can perceive without obtaining a profound "reaction value." The actual reaction value, or meaning, must depend on a mnemic synthesis resultant from past experience obtained from similar classes of signals. In an operational sense, it would appear to be more effective if the use of "subconscious" mechanisms [8] would be discarded in the formulation of the "body schema" and replaced by the figure-background concept of Goldstein.[9] In the latter formulation the phenomena that are not of recognized importance in immediate awareness constitute the matrix on which the meaningful signals or symbols are generated. Such a formulation obviates recourse to quasimystical terminology.

Denny-Brown, Meyer, and Horenstein [3] showed that in a subject with profound lateral dominance, the dominance (or extinction) could be erased if sufficient quantity of stimulation (spatial summation) was applied to the uninvolved side. I have recently confirmed this observation in several patients. It is interesting to note parenthetically that in normally sentient persons differential intensity stimuli of the order of 20:1 are still easily and repeatedly resolved. From the observation of the effect of quantity of stimulation as a factor in extinction phenomena, it would appear that clinical lateral dominance might be adequately explained on the basis of insufficient excitation of the perceptual apparatus on the involved side in the response to simultaneous bilateral stimulation. That is, if one side received a fivefold greater signal strength than the other side, the less stimulated side need not attain a threshold for perception; hence only the stimulus on the uninvolved side would be reported when two stimuli of approximately equal intensity were applied simultaneously to a brain-injured subject. It should be clearly recognized, however, that in the lateral extinction process this spatial summation is a particularization of the general sensory law that, under conditions of disturbed afferent inflow, stimulation over a wider area and of greater intensity enhances signal reception and perception. This law apparently holds irrespective of whether the perceptual difficulty arises as the result of a lesion in the peripheral or the central anatomical structures. Although this quantitative statement appears to be an eminently adequate explanation for lateral dominance, it does not furnish a workable hypothesis for the pattern of rostral, or face, dominance. For the pattern of rostral dominance of perception the body image concept becomes a natural solution.

CONCLUSIONS

It is proposed that the pattern of ipsilateral clinical extinction is intimately associated with the body image concept of the subject. In the child, clinical ipsilateral extinction represents an unprecise concept of the body image; in the case of the adult with a brain lesion, when clinical ipsilateral extinction is elicited, a regressive [10] simplification of the body image concept into the childhood pattern is hypothesized.

8. Smythies, J. R.: The Experience and Description of the Human Body, Brain **76**:133-145, 1953.

9. Goldstein, K.: Language and Language Disturbances: Aphasic Symptom Complexes and Their Significance for Medicine and Theory of Language, New York, Grune & Stratton, Inc., 1948, p. 374.

10. Fink, M., and Bender, M. B.: Perception of Simultaneous Tactile Stimuli in Normal Children, Neurology **3**:27-34, 1953. Jaffe, J., and Bender, M. B.: The Factor of Symmetry in the Perception of 2 Simultaneous Cutaneous Stimuli, Brain **75**:167-176, 1952.

USE OF PHENACEMIDE (PHENURONE) IN TREATMENT OF NARCOLEPSY AND CATAPLEXY

A Preliminary Report

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ALTHOUGH the pathogenesis and pathophysiology of idiopathic narcolepsy remain obscure, it is known that symptomatic forms may follow head injury, cerebral arteriosclerosis, encephalitis lethargica, and intracranial tumors involving the posterior portion of the hypothalamus. Ranson [1] in 1939 produced somnolence in monkeys with lesions limited to the subthalamus and hypothalamus. It remained, however, for the recent studies of Magoun and his co-workers [2] clearly to show that afferent stimulation of the ascending activating system of the brain stem underlies wakefulness, while absence of this influence results in sleep. An arousal reaction, or state of wakefulness, was produced by stimulation of the dorsal portion of the hypothalamus, the subthalamus, the related medial bulbar reticular formation, or the tegmentum of the pons and midbrain. Lesions of the ventral portion of the diencephalon and the tegmentum of the midbrain, within the area of distribution of the ascending reticular activating system, produced recurrent electroencephalographic spindle bursts like those of normal sleep. It would appear that this mechanism may be involved in narcolepsy.

Though they are less precise in their neurophysiological significance, it is nevertheless important to remember that cataplexy and, less commonly, sleep paralysis, hypnagogic hallucinations, and somnambulism are often associated with narcolepsy. Cataplexy is a transient flaccid paresis without loss of consciousness, and sleep paralysis is similar except that it occurs while the patient is either drowsing off or awakening. Cataplexy is precipitated by emotion, like laughter and anger; and sleep paralysis is associated with tense anxiety, perhaps having been precipitated by an unpleasant dream, which awakens the patient, frightened and paralyzed. Hypnagogic hallucinations usually occur when the patient is falling asleep or in a drowsy state and are generally of a vivid and terrifying character. Somnambulism consists of

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1. Ranson, S. W.: Somnolence Caused by Hypothalamic Lesions in Monkey, Arch. Neurol. & Psychiat. **41**:1-23 (Jan.) 1939.

2. Magoun, H. W.: The Ascending Reticular Activating System, A. Res. Nerv. & Ment. Dis., Proc. **30**:480-492, 1950. Moruzzi, G., and Magoun, H. W.: Brain Stem Reticular Formation and Activation of the EEG, Electroencephalog. & Clin. Neurophysiol. **1**:455-473 (Nov.) 1949.

automatisms when the patient is partially asleep. Presumably, this involves a state of limited integration in which a portion of the cortex is not functioning properly with respect to the rest of the brain. Since the automatisms of "psychomotor states" likewise involve a state of limited integration in which the temporal lobe is preoccupied in a convulsive disorder, it may be that these conditions are related. The close interrelationships between the sleeping state and emotional factors in all the conditions associated with the narcolepsy-cataplexy complex strongly suggest a dysfunction of the hypothalamus and its connecting pathways or associated centers in the diencephalon, and possibly the temporal lobes.

It is of interest in regard to the possible pathogenesis of cataplexy that an inhibition of muscular tonus has been demonstrated by Magoun [3] and Magoun and Rhines [4] with stimulation of the bulbar reticular formation. This mechanism has been further studied by Granit and Kaada [5] and has been related to postural reflexes, in which the efferent gamma system of Leksell [6] is the motor component of the reflex arc and the muscle spindle afferent fibers constitute the proprioceptive component. The transient paresis of cataplexy in association with emotional crises and of sleep paralysis in association with drowsiness would appear to fit in with the inhibition of muscular tonus obtained with stimulation of the bulbar reticular formation or its more rostral associated tracts and centers.

Lindsley [7] has discussed the relation between the descending influences of the reticular facilitatory system and the reticular inhibitory system and suggests that inhibition of the former would produce a disturbance of the balance between these two systems comparable to a stimulation of the inhibitory system. He points out that the region of the lower brain stem, from which these descending influences arise, is also the site of the ascending reticular activating system concerned with wakefulness, and that physiological blockage of these systems in the tegmentum of the midbrain might result not only in sleep but in a temporary predominance of the lower reticular inhibitory system. It is conceivable that sleep paralysis might be explained on this basis. On the other hand, a primary stimulation of the bulbar inhibitory system, as indicated, might also produce sleep paralysis and cataplexy. The stimulus of emotion during sleep, such as might be produced by a terrifying dream, for example, would act not only to cause the sleep paralysis but also to awaken the patient. The stimulus of emotion on the same system during the waking state presumably would produce cataplexy and a concomitant state of heightened consciousness.

The paroxysmal character of narcolepsy and its allied states led Kinnier Wilson [8] and others to relate these conditions to epilepsy. The validity of such a relationship is by no means clear, and it would appear that the narcolepsy-cataplexy complex

3. Magoun, H. W.: Bulbar Inhibition and Facilitation of Motor Activity, Science **100**:549-550 (Dec. 15) 1944.

4. Magoun, H. W., and Rhines, R.: An Inhibitory Mechanism in the Bulbar Reticular Formation, J. Neurophysiol. **9**:165-171 (May) 1946.

5. Granit, R., and Kaada, B. R.: Influence of Stimulation of Central Nervous Structures on Muscle Spindles in Cat, Acta physiol. scandinav. **27**:130-160, 1953.

6. Leksell, L.: Action Potential in Excitatory Effects of the Small Ventral Root Fibers to Skeletal Muscle, Acta physiol. scandinav. (Suppl. 31) **10**:1, 1945.

7. Lindsley, D. B.: Brain-Stem Influences on Spinal Motor Activity, A. Res. Nerv. & Ment. Dis., Proc. **30**:174-195, 1950.

8. Wilson, S. A. K.: Neurology, Baltimore, William Wood & Company, 1940.

may best be thought of as a paroxysmal dysfunction of hypothalamic and subthalamic nuclei and their neurophysiologically associated tracts and centers, as outlined above.

Levin's [9] explanation of cataplexy in terms of a conditioned inhibition is of interest but fails to consider what centers are inhibited or the neurophysiological mechanism of inhibition. Also, since it involves a transient dysfunction of the central nervous system, Levin's theory and the neurophysiological concepts advanced above are by no means mutually exclusive.

Treatment of the narcolepsy-cataplexy complex has not been entirely satisfactory. Amphetamine and other sympathomimetic agents have proved moderately successful in treatment of narcolepsy but have had little or no effect on cataplexy. In 1943 Dynes [10] reported that potassium therapy was effective in cataplexy. A recent communication from Dynes,[11] however, indicates that on further follow-up observation of his patients the effect of potassium therapy on cataplexy has been difficult to evaluate.

Although a metabolic dysfunction might underlie prolonged paresis, such as that found in periodic familial paralysis, it is difficult to envision such a mechanism in cataplexy, which starts abruptly and lasts but a few seconds. It would appear that an additional factor must be present in cataplexy, even though a dysfunction of potassium metabolism were present as a conditioning mechanism. The additional factor, presumably, would be a neurogenic one, as suggested by the other phenomena associated with cataplexy and by the neurophysiological evidence previously mentioned. Insulin hypoglycemia has been reported as a successful method of treatment of narcolepsy and sleep paralysis.[12] Although such a form of therapy would appear to be unwarranted for the majority of patients with these conditions, it is, nevertheless, of interest that it was tried on the assumption that these conditions involved a physiological disturbance of the hypothalamus, which "is one of the targets of insulin hypoglycemia."

The recent introduction of a new anticonvulsant, phenacemide [13] (Phenurone; phenacetylcarbamide), which possesses unique effectiveness in temporal lobe epilepsy and which is secondarily effective in petit mal of presumable diencephalic origin, as well as in other types of convulsive disorders, suggested the possibility of using this agent to advantage in the narcolepsy-cataplexy complex. The fact that phenacemide ordinarily has no sedative effect, and may even cause insomnia in some patients, further contributed to the selection of this drug for trial in narcolepsy.

CLINICAL STUDY AND RESULTS

Six patients were selected, but it has been possible to follow closely the course over the past year in only five. Although the number of patients studied has necessarily been small, the results have been sufficiently striking to warrant the present preliminary report.

9. Levin, M.: Aggression, Guilt and Cataplexy, A. M. A. Arch. Neurol. & Psychiat. **69**:224-235 (Feb.) 1953.

10. Dynes, J. B.: Cataplexy and Its Treatment, J. Nerv. & Ment. Dis. **98**:48-55 (July) 1943.

11. Dynes, J. B.: Personal communication to the authors.

12. Weitzner, H.: Sleep Paralysis Successfully Treated with Insulin Hypoglycemia, A. M. A. Arch. Neurol. & Psychiat. **68**:835-841 (Dec.) 1952.

13. Tyler, M., and King, E. Q.: Phenacemide in Treatment of Epilepsy, J. A. M. A. **147**:17-21 (Sept. 1) 1951.

All five patients had the idiopathic type of disease. All presented both narcolepsy and cataplexy; three exhibited hypnagogic hallucinations, and one, sleep paralysis. In no case did neurological examination reveal any abnormality.

The electroencephalograms were of considerable interest in showing tracings which were essentially within the limits of normal when the patient was awake and resting, but which showed a slight, generalized cerebral dysrhythmia of nonspecific type when the patient drowsed off. The dysrhythmia was of the type usually associated with drowsiness and tended to recur repeatedly, especially in the later portion of the resting record. In all cases, except in one of two tests on one patient, the tracings cleared and appeared normal with hyperventilation. No definite focal changes were found in the records.

The main clinical features and results obtained are shown in the accompanying Table.

The results indicate a striking effect of phenacemide on cataplexy and a less striking effect on narcolepsy in three out of four patients, if the subject with questionable toxicity is eliminated from consideration.

The striking effect of phenacemide therapy may be illustrated in the case of Patient W. K., a 33-year-old high school teacher, who began at the age of 14 to have both narcolepsy and cataplexy. For example, when he was drilling in the Army a few years before, his head would

Clinical Results of Phenacemide (Phenurone) Therapy in the Narcolepsy-Cataplexy Complex*

Patient	Age	Sex	Duration, Yr.	Result			
				No Effect	Toxic Reaction	Narcolepsy	Cataplexy
N. S.	38	F	18	Questionable	—	—	—
A. Mal.	38	M	20	—	Questionable	Better (?) on drug t. i. d.	Rare attacks (?) on drug t. i. d.
A. Med.	39	M	14	—	—	Slightly improved	Markedly improved
C. H.	28	M	7	—	—	Moderately improved	No attacks
W. K.	33	M	17	—	—	Markedly improved	No attacks

* Dose 0.5 gm. four times a day.

suddenly fall forward and, if he was not aroused by a fellow soldier at his side, he would fall asleep for a few seconds. While asleep he usually had a short, and very vivid, dream of a frightening nature. He stated that for the most part he felt as though he were aware of what was going on about him even when "asleep and dreaming" but that he was powerless to control the situation.

The patient sought aid, since his more recent position as a teacher was in jeopardy. In addition to his attacks of narcolepsy, which occurred three or four times a day in his classroom, he was embarrassed by his cataplectic spells in moments of emotional tension, such as when he was disciplining a recalcitrant pupil. On these occasions he would sink to the floor, usually in a squatting position, and remain thus for a few moments, until his emotion abated and his strength returned. His difficulty soon became apparent to the authorities, and he had been advised that he could no longer be permitted to continue teaching if the episodes persisted.

The patient was given phenacemide, 0.5 gm. four times a day. In approximately 2 weeks he noted definite improvement in his narcolepsy, and in 10 months of treatment he has had no further episodes of cataplexy, although he has been exposed to sufficient provocation in connection with his work as a junior high school teacher. He stated that recently he had been faced in the classroom with a particularly difficult disciplinary problem. The situation was especially charged with emotion inasmuch as the student threatened to strike him. Much to the patient's joy, he was able to cope with the situation without experiencing a cataplectic attack. It was just in this sort of emotional situation that an attack had invariably occurred previously. The episodes of narcolepsy have been reduced to rare episodes, and these occur, as a rule, in the late afternoon. His improvement has been sufficient that the patient now feels that he lives an essentially normal life. Recently he received an advance in position. It is also of interest to note that

when on one occasion he inadvertently ran out of his medication he experienced a definite recurrence of his narcolepsy and cataplexy. Careful evaluation of his blood and hepatic function has never showed abnormalities.

COMMENT

Clinical and electroencephalographic evidence suggests that narcolepsy consists of a transient dysfunction of the neurophysiological mechanism underlying wakefulness in an otherwise essentially normal person. The recurrent character of the dysfunction suggests a failure of some regulating mechanism, presumably involving the ascending reticular activating system in the ventral portion of the diencephalon, in view of the nature of the other clinical phenomena usually associated with narcolepsy. The effect of phenacemide on narcolepsy might be explained either in terms of direct stimulation of the ascending reticular activating system or of a regulating effect on associated tracts and centers in the diencephalon and related structures, the dysfunction of which would be to produce a temporary blocking of this system.

From the standpoint of the balanced condition between the reticular facilitatory and reticular inhibitory systems envisioned by Lindsley,[7] however, a stimulatory effect of phenacemide on the ascending reticular activating system (an assumption essential to explain its beneficial effect in narcolepsy) might also act to stimulate the (descending) reticular facilitatory system and thus tend to counteract any hypotonic or paretic effect that might be produced by the activity of the reticular inhibitory system. Or, again, on the same basis, an inhibitory effect of phenacemide on the bulbar reticular inhibitory system might block those transient stimulations presumably causing cataplexy and sleep paralysis and, at the same time, produce hyperactivity of the reticular activating system sufficient to prevent narcolepsy. The primary importance of narcolepsy in the narcolepsy-cataplexy complex would seem to support the first thesis. On the other hand, the primary effectiveness of phenacemide on cataplexy rather than on narcolepsy would speak for the second hypothesis, namely, an inhibitory effect of the drug on the reticular inhibitory system. A third possibility, perhaps the most likely, would be that phenacemide has a regulating effect on structures of the diencephalon and brain stem, which serves to control the transient dysfunction of associated tracts and centers by acting upon the reticular activating system, in the case of narcolepsy, and upon the reticular inhibitory system, in the case of cataplexy.

It is of interest that the predominant effect of phenacemide is the opposite of that usually obtained with the sympathomimetic agents, such as amphetamine, which primarily help narcolepsy but have little or no effect on cataplexy. The stimulating effect of emotion on the sympathetic nervous system (sympathomimetic action) and, secondarily, upon the reticular inhibitory system, if the foregoing analysis of cataplexy is correct, suggests the same difference, since the action of phenacemide was postulated as an inhibitory one on the reticular inhibitory system. The practical importance of this point is well illustrated in the case of Patient C. H., whose narcolepsy was fairly well controlled with methamphetamine (Desoxyn) but whose cataplexy was little benefited by this and similar agents he had tried. Phenacemide alone practically controlled his cataplexy, as was the case with Patient W. K., but he still required methamphetamine for his narcolepsy. On this basis, a trial of phenacemide in combination with sympathomimetic drugs would appear indicated in cases in which the disorder is not controlled by phenacemide alone.

SUMMARY

The therapeutic effectiveness of phenacemide (phenylacetylcarbamide) on the narcolepsy-cataplexy complex has been demonstrated in three out of four patients who tolerated this agent. Phenacemide would appear to be effective primarily against cataplexy and secondarily against narcolepsy. The neurophysiological basis of narcolepsy and its allied states is discussed in terms of clinical and pathological facts, recent neurophysiological research, and the electroencephalographic findings in these conditions, as well as the probable mode of action of phenacemide on the complex, as observed in this study.

ELECTROSHOCK AND THE RAT ADRENAL CORTEX

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THERE have been many clinical studies on the blood eosinophile and lymphocyte levels in patients following electroshock therapy.[1] All seem to agree that there is a definite fall, similar in most ways to that seen after corticotropin or epinephrine administration. Altschule and associates [2] state that the degree of fall tends to decrease as therapy is continued for long periods.

Hoagland, Pincus and associates [3]; Early, Hemphill, and associates,[4] and Ashby [5] have demonstrated adrenocortical activation following electroshock in the

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1. (*a*) Graham, B. F., and Cleghorn, R. A.: Changes in the Circulating Leucocytes Following Electrically Induced Convulsions in Man, J. Clin. Endocrinol. **11**:1469, 1951. (*b*) Hoagland, H.; Calloway, E.; Elmadjiam, F., and Pincus, G.: Adrenal Cortical Responsivity of Psychotic Patients in Relation to Electroshock Treatments, Psychosom. Med. **12**:73, 1950. (*c*) Mikklesen, W. P., and Hutchins, T. T.: Lymphopenia Following Electrically Induced Convulsions in Male Psychotic Patients, Endocrinology **42**: 394, 1948. (*d*) Parsons, E. H.; Gildea, E. F.; Ronzoni, E., and Hulbert, S. Z.: Comparative Lymphocytic and Biochemical Responses of Patients with Schizophrenia and Affective Disorders to Electrochock, Insulin Shock and Epinephrine, Am. J. Psychiat. **105**:573, 1949. (*e*) Rees, L.: Physiological Concomitants of Electronarcosis, J. Ment. Sc. **95**:162, 1949. (*f*) Stern, K.; Askonas, B. H., and Cullen, A. M.: Influence of Electroconvulsive Treatment on Blood Sugar: Total Number of Leucocytes and Lymphocytes, Am. J. Psychiat. **105**:585, 1949.

2. Altschule, M. D.; Parkhurst, B. S., and Tillotson, K. J.: Decreases in Blood Eosinophilic Leukocytes After Electrically Induced Convulsions in Man, J. Clin. Endocrinol. **9**:440, 1949.

3. Hoagland, H.; Malamud, W.; Kaufman, I. C., and Pincus, G.: Changes in the Electroencephalogram and Excretion of 17-Ketosteroids Accompanying Electroshock Therapy of Agitated Depression, Psychosom. Med. **8**:246, 1946. Hoagland, H., and Pincus, G.: Pituitary-Adrenocortical Function in Patients with Severe Personality Disorders, Proceedings of the First Clinical ACTH Conference, edited by John R. Mote, Philadelphia, The Blakiston Company, 1950, p. 544.

4. Early, D. F. M.; Hemphill, R. E.; Meggs, R.; Reiss, M.; Steele, G. D. F.; Cook, E. R., and Pelly, J. E.: The Use of ACTH in Psychiatry; abstracted, J. Endocrinol. **7**:xviii, 1951.

5. Ashby, W. R.: Effects of Electroconvulsive Therapy on Excretion of Cortins and Ketosteroids, J. Ment. Sc. **95**:275, 1949.

changes in the urinary 17-ketosteroids, uric acid, inorganic phosphate, sodium, potassium, and neutral reducing lipid. Hoagland, Pincus and associates [1b] state that these changes can also be produced with subconvulsive electroshock and claim that each electroshock is equivalent in effect to 100 mg. of corticotropin, while Early and associates [4] state that one electroshock "mobilizes more than 50 mgm. of ACTH." On the other hand, Simon, Bowman, and Halliday [6]; Katzenelbogen and associates,[7] and Altschule and Parkhurst [8] find no evidence of increased excretion of 17-ketosteroids or other urinary changes.

Although a great deal of animal experimentation [9] has been done on the behavioral changes following electroshock, there has been relatively little investigation of the relationship of these changes to the endocrine effects. However, Rosvold and associates [10] have demonstrated a significant hypertrophy of the adrenal cortex in rats during conditions of electroshock known to alter behavior. That this is a functional hypertrophy is indicated by the fact that in a resting state the ascorbic acid content of the enlarged adrenals is increased proportionately as the gland enlarges. This hypertrophy of the adrenal cortex does not take place when the animal receives premedication with pentobarbital (Nembutal), a circumstance which also inhibits the behavioral changes.

Ellis and Wiersma [11] have shown a similar adrenocortical hypertrophy following electronarcosis in dogs and guinea pigs. They have also found hypertrophy of the thyroid and ovaries, as well as an increase in the thyrotropic and gonadotropic activity of the animals' serum. Recently, two Italian investigators, Novelli and Massini,[12] have demonstrated postelectroshock hypertrophy of the adrenals and thyroid in dogs.

The primary purpose of the present investigation is to add evidence concerning the effect of electroshock on the adrenal cortex. An attempt was made to reproduce

6. Simon, A.; Bowman, K. M., and Halliday, N.: Studies in Electronarcosis Therapy: Physiological Effects in Electronarcosis and Electroshock, J. Nerv. & Ment. Dis. **107**:358, 1948.

7. Katzenelbogen, S.; Bauer, A. K., and Coyne, A. R. M.: Electroshock Therapy: Clinical, Biochemical and Morphological Studies, Arch. Neurol. & Psychiat. **52**:323, 1944.

8. Altschule, M. D.: Physiologic Observations in Mental Disease, Bull. New England M. Center **11**:229, 1949. Altschule, M. D., and Parkhurst, B. H.: Effect of Treatment on Excretion of 17-Ketosteroids in Patients with Mental Disease, Arch. Neurol. & Psychiat. **64**:516, 1950.

9. (*a*) Golub, L. M., and Morgan, C. T.: Patterns of Electrogenic Seizures in Rats: Their Relation to Stimulus Intensity and to Audiogenic Seizures, J. Comp. Psychol. **38**:239, 1945. (*b*) Hayes, K. J.: Cognitive and Emotional Effects of Electroconvulsive Shock in Rats, J. Comp. & Physiol. Psychol. **41**:40, 1948. (*c*) Porter, P. B., and Stone, C. P.: Electroconvulsive Shock in Rats Under Ether Anesthesia, ibid. **40**:441, 1947. (*d*) McGinnies, E., and Schlosberg, H.: Effects of Electroshock Convulsions on Double Alternation Lever-Pressing in the White Rat, J. Exper. Psychol. **35**:361, 1945. (*e*) Rosvold, H. E.: Effects of Electroconvulsive Shocks on Gestation and Maternal Behavior: I, J. Comp. & Physiol. Psychol. **42**:118, 1949; (*f*) Effects of Electroconvulsive Shocks on Gestation and Maternal Behavior: II, ibid. **42**:207, 1949.

10. Rosvold, H. E.; Kaplan, S. J., and Stevenson, J. A. F.: Effects of Electroconvulsive Shock on the Adrenal Cortex, Proc. Soc. Exper. Biol. & Med. **80**:60, 1952.

11. Ellis, C. H., and Wiersma, C. A. G.: Influence of Electronarcosis on the Secretory Activity of the Pituitary Gland, Proc. Soc. Exper. Biol. & Med. **58**:160, 1945.

12. Novelli, A.: Prime osservazioni sulle capsule surrenale di cani sottoposti ad elettroshock, Boll. Soc. ital. biol. sper. **25**:1351, 1949. Novelli, A., and Massini, A.: Osservazioni sulla ghiandola tiroide di cuccioli sottoposti ad elettroshock, ibid. **26**:1333, 1950.

the postshock adrenocortical hypertrophy previously reported[10] and the adrenal ascorbic acid findings suggestive that this is a functional hypertrophy. It was further intended to determine the role of electroshock as an adrenocortical activator by demonstrating its ability to cause an acute fall in the ascorbic acid and cholesterol content of the gland, similar to that caused by the administration of corticotropin and of epinephrine and various other stresses which presumably are mediated through endogenous corticotropin.[13]

Moreover, an attempt was made to gain some knowledge of the mechanism by which electroshock exerts its endocrine effects. The role of the convulsion itself was studied by determining, after nonconvulsive electroshocks, whether the endocrine changes occur. Although the administration of this type of shock presented a difficult technical problem, two approaches offered the most promise: (*a*) the use of specifically selected anticonvulsant drugs chosen for their site of action (mainly spinal cord) and relatively low toxicity, and (*b*) the use of a preliminary electroshock convulsion as an anticonvulsant agent for further electroshocks administered immediately thereafter.

Finally, an attempt was made to evaluate the role of endogenous epinephrine in electroshock by utilizing an essentially adrenodemedullated preparation: a rat with an intraocular adrenal transplant which was adrenal cortex tissue alone. These animals had, like others which received no transplant, been previously adrenalectomized.

METHODS

Animals.—Adult male albino rats of the Sprague-Dawley strain were housed in individual cages in a constant-temperature room maintained at 78 F. Purina Laboratory Chow and water were provided ad libitum. All animals were weighed and handled daily in a one-week period of acclimatization to the aforedescribed conditions prior to experimental treatment.

Procedures.—1. Administration of Electroshock: The method was that of Rosvold and associates,[10] which consisted of 50 ma. delivered for 0.2 second through padded clip electrodes attached to the animal's ears. The electrodes were soaked in sodium bicarbonate solution to facilitate passage of current. This procedure induced a convulsion, as described by Golub and Morgan.[9a]

2. Adrenal Weights: All animals were weighed daily. Twenty-four hours following the final experimental treatment, except when otherwise stated, the animals were anesthetized with pentobarbital in saline given intraperitoneally. Both adrenals were removed, cleaned by dissection, and weighed to the nearest one-tenth milligram. Depending on the purpose of the experimental group, the glands were placed in one of the following solutions: 6% trichloracetic acid for ascorbic acid determination, acetone-alcohol solution for cholesterol determination, or 10% formalin for histological study.

3. Administration of Anticonvulsant Drugs: Two preparations, mephenesin and DEP (diethyl-propanediol)[14] were used. These drugs were chosen because their primary site of

13. (*a*) Long, C. H. N.: Relation of Cholesterol and Ascorbic Acid to the Secretion of the Adrenal Cortex, Recent Progr. Hormone Res. **1**:99, 1946; Conditions Associated with the Secretion of the Adrenal Cortex, Federation Proc. **6**:461, 1947. (*b*) Sayers, G. ,and Sayers, M. A.: The Pituitary-Adrenal System: The Adrenal Cortex, Ann. New York Acad. Sc. **51**:522, 1949.

14. Mephenesin, provided by E. R. Squibb and Sons under the trademark Tolserol, is a colorless, odorless, crystalline solid with a melting point of 70 to 71 C. Its solubility at 22 C. is 1.09 gm. per 100 cc., but relatively stable supersaturated solutions can be prepared. It is highly soluble in ethyl alcohol and propylene glycol. Solutions of the drug are compatible and freely miscible with isotonic sodium chloride solution. The drug is both anticonvulsant

(Footnote continued on next page)

action seems to be the spinal cord and lower brain centers and also because of their relatively low toxicity. A dose of 2.2 cc. of a 2% solution of mephenesin or 1.2 cc. of a 5% solution of DEP was injected intraperitoneally.

4. Determination of Adrenal Ascorbic Acid and Cholesterol Levels: The majority of the adrenal glands were analyzed for ascorbic acid content, and this was done by the method of Roe and Kuether.[15] A small group of adrenals were also studied for cholesterol content, and these determinations were made by the method of Sperry and Brand[16] as modified by Mylon.[17]

5. Histological Study: The adrenals used in this phase of the experiment were preserved in 10% formalin for at least two weeks prior to section. The tissues were then placed on a freezing microtome, sectioned while frozen, and stained with scarlet red (Sudan IV) for lipid content.

6. Adrenalectomy and Intraocular Transplantation: Rats were adrenalectomized bilaterally under ether anesthesia and were then supported on saline drinking water. Some of these animals were then given intraocular transplants of whole newborn-rat adrenals, using the method of Greene[18] as recently described by Patino.[19] The transplants were allowed to develop for two weeks prior to experimental manipulation of these animals.

Experimental Groups.—1. Electroshock Every Eight Hours: A group of five animals were shocked three times daily, at 8 a. m., 4 p. m., and midnight, for 10 days.

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and paralytic in action, the chief site of which seems to be the internuncial neurons of the spinal cord, although the lower brain centers are probably involved also to some degree. It protects against both chemically and electrically induced convulsions. At concentrations of 10% and above, administration of the drug by any route is often followed by hemoglobinuria, hemoglobinemia, respiratory and cardiac depression, and other toxic effects; but when it is given in 2% solution or less, there is little or no toxicity. (Berger, F. M.: Spinal Cord Depressant Drugs, J. Pharmacol. & Exper. Therap. **96**:243, 1949.)

DEP (2, 2-diethyl-1,3-propanediol), provided by Dr. F. M. Berger of the Wallace Laboratories, is a white, crystalline solid with a melting point of 62 to 62.5 C. The drug is still in experimental use only, and the preparation used here was made by the reaction of 2-ethylbutyraldehyde and formaldehyde in alcoholic potassium hydroxide solution. Its solubility in water is 10.6 gm. per 100 ml. at 23 C. Solutions of the drug are stable and can be sterilized by heating. The drug has anticonvulsant and paralytic properties, but the former is much stronger than the latter. Toxic effects, when the drug is used in concentrations of 10% or less, are minimal (Berger, F. M.: Anticonvulsant Action of 2-Substituted-1, 3-Propanediols, Proc. Soc. Exper. Biol. & Med. **71**:270, 1949; Anticonvulsant Activity of 2,2-Disubstituted-1,2-Propanediols in Electroshock Seizures, ibid. **78**:277, 1951. Berger, F. M.; Ludwig, B. J., and Russo, C.: Pharmacological Properties of DEP, Federation Proc. **9**:258, 1950).

Although it was not known, prior to undertaking the experiments reported here, that these drugs in essentially nontoxic doses could cause a pronounced adrenal hypertrophy, such a conclusion seems warranted from the experimental data. This property of the drugs has made them of little value for the purposes for which they were used here. However, in a personal communication from R. J. Perchard, of E. R. Squibb & Sons, it was stated that this adrenal-activating property of mephenesin has been applied in very recent experiments intended to demonstrate the antiarthritic effect of the drug in a manner similar to that of corticotropin.

15. Roe, J. H., and Kuether, C. A.: Determination of Ascorbic Acid in Whole Blood and Urine Through the 2,4-Dinitrophenylhydrazine Derivative of Dehydroascorbic Acid, J. Biol. Chem. **147**:399, 1943.

16. Sperry, W. M., and Brand, F. C.: Colorimetric Determination of Cholesterol, J. Biol. Chem. **150**:315, 1943.

17. Mylon, E.: Personal communication to the authors.

18. Greene, H. S. N.: Use of the Mouse Eye in Transplantation Experiments, Cancer Res. **7**:491, 1947.

19. Patino, J. F.: Studies on the Transplantation of Embryonic Endocrine Tissues, Thesis, Yale University School of Medicine, 1952.

2. Electroshock Every 24 Hours: A group of seven animals were shocked once daily for 10 days.

3. Untreated Controls: A group of five animals were maintained under conditions exactly similar to the preceding groups except that no experimental manipulations were performed other than daily weighing and attachment of electrodes to the ears. No shock was delivered.

4. DEP and Electroshock: A group of five animals were given injections of DEP once daily for 10 days. As soon after each injection as the righting reflex disappeared, usually within two minutes, shock was administered. Although the initial jump remained, all other phases of a normal convulsion were absent, and the animal lay motionless and areflexic for a variable period, from 5 to 20 minutes.

5. DEP Alone (Control for Effect of Drug): A group of five animals were given injections of DEP once daily for 10 days.

6. Mephenesin and Electroshock: A group of five animals were given injections of mephenesin once daily for 10 days. As soon after each injection as the righting reflex was lost, usually within two to three minutes, shock was administered, and the response here was exactly the same as that after injection of DEP.

7. Mephenesin Alone (Control for Effect of Drug): A group of five animals received injections of mephenesin once daily for 10 days.

8. Saline Alone (Control for Stress of Injection and Fluid Volume of Drug): A group of seven animals received injections once daily for 10 days of isotonic saline intraperitoneally in amounts similar to those used with injection of the anticonvulsant drugs.

9. Saline and Electroshock (Control for Stress of Injection and Fluid Volume of Drug in Shocked Animals): A group of five animals received injections of isotonic saline and were then shocked once daily for 10 days.

10. Multiple Shock Convulsions: A group of seven animals were given a preliminary course of 10 daily electroshocks. For 10 days following this they were given daily multiple shock convulsions; that is, 50 ma. of current was delivered for 0.2 second, and, while the animal was in the tonic-extension phase of a typical convulsive response, 10 additional shocks were administered rapidly over a five-second period. As had been expected from the work of Toman and associates[20] these additional shocks in no way altered the pattern of convulsions described as following one shock.

11. Controls for Multiple Shock: Seven animals were given a preliminary course of 10 daily electroshocks, similar to those in the preceding group, and were then given single daily electroshocks for 10 days.

12. Acute Effects of Single Electroshock: A group of 14 animals was studied for acute chemical and histological changes in the adrenal following a single electroshock. Two animals were killed just prior to the shock and served as controls, and two animals were killed at each of the following time intervals after the administration of the single shock: 1, 2½, 4½, 9, 24, and 48 hours. Of the four adrenals removed at each time interval, two were retained for ascorbic acid determination, one for cholesterol determination, and the fourth for histological study.

13. Adrenalectomized and Intraocular Transplants: A group of six animals were adrenalectomized, and three of these received intraocular transplants of newborn-rat adrenals. After two weeks these three animals received a series of daily electroshocks for 10 days. All received saline drinking water during this period.

RESULTS

Effects of Electroshock on Adrenal Weight.—It is indicated in Table 1 that both the group given one shock a day for 10 days and the group given three shocks a day for 10 days had adrenals significantly heavier than did the unshocked controls. It may be concluded that the effect of a series of electroshocks is significantly to

20. Toman, J. E. P.; Swinyard, E. A., and Goodman, L. S.: Properties of Maximal Seizures and Their Alteration by Anticonvulsant Drugs and Other Agents, J. Neurophysiol. **9**:231, 1946.

increase adrenal weights in rats. The difference between the one-shock- and the three-shock-a-day group is not significant. That the increases are not due to a rise in body weight is shown in Table 2, which compares the net gain or loss in weight

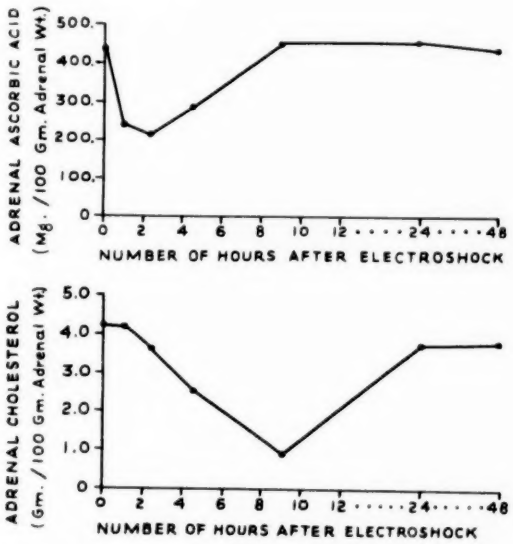
TABLE 1.—*Comparison of Mean Adrenal Weights in Groups Receiving Electroshock Alone*

Experimental Group	No.	Mean Adrenal Weight, Mg.	Mean Difference	t	P*
1. Shock 3 × daily	4	23.3	(1 vs. 3) 5.9	4.6	< 0.01
2. Shock 1 × daily	7	21.5	(1 vs. 2) 1.8	1.3	> 0.05
3. Untreated controls	5	17.4	(2 vs. 3) 4.1	3.0	< 0.01

* P levels calculated on one tail of the distribution curve.

TABLE 2.— *Mean Body Weight Differences, Expressed in Grams*

Groups Compared	Difference	Degrees of Freedom	t	P
Initial weights of electroshock groups vs. nonelectroshock group	— 5	7	1.4	> 0.05
Final weights of electroshock groups vs. nonelectroshock group	41	7	16.4	< 0.01



Upper, adrenal ascorbic acid concentration during the 48 hours after electroconvulsive shock. Lower, adrenal cholesterol concentration during the 48 hours after electroconvulsive shock.

for each group and shows, in fact, that there was a slight loss of body weight among all groups given electroshock.

Acute Effects of a Single Electroshock.—Ascorbic Acid and Cholesterol Content of the Adrenal: It is shown in the accompanying Chart that the fall in adrenal ascorbic acid and cholesterol concentration during the 48-hour period following a

single electroshock is typical of that found after many other types of stress.[21] The only exception is that the fall in cholesterol concentration is slower. In Table 3 are presented the results of the cholesterol and ascorbic acid determinations. It is clear that one electroshock rapidly mobilizes corticotropin.

Histological Changes: Results of the studies carried out to illustrate lipid depletion by staining histological sections with scarlet red were equivocal. There was no demonstrable change in the amount or location of sudanophilic material in adrenals taken at the time intervals indicated.

TABLE 3.—*Mean Adrenal Cholesterol and Ascorbic Acid Concentrations Before and After Electroshock*

Time Animal Was Killed	Adrenal Ascorbic Acid, Mg./100 Gm.	Adrenal Cholesterol, Gm./100 Gm.
Before shock	443	4.2
After shock		
1 hr.	245	4.2
2½ hr.	231	3.7
4½ hr.	290	2.5
9 hr.	458	0.8
24 hr.	458	3.8
48 hr.	441	3.8

TABLE 4.—*Comparison of Mean Adrenal Ascorbic Acid Concentrations in Groups Receiving Electroshock Alone*

Experimental Group	No.	Mean Adrenal Ascorbic Acid, Mg./100 Gm.	Mean Difference	t	P
Shock 3 × daily	4	452	(1 vs. 3) 11	0.5	>0.50
Shock 1 × daily	7	494	(1 vs. 2) 42	1.9	>0.05
Untreated controls	5	463	(2 vs. 3) 31	1.3	>0.05

Effect of Continued Electroshock (Ten Days) on Adrenal Ascorbic Acid.—In Table 4 it is shown that the concentration of ascorbic acid in adrenals removed 24 hours after the last shock following 10 days of treatment was not significantly different from that in the adrenals of untreated controls. However, since the adrenal weight is increased in the shocked animals, there is actually a greater amount of total adrenal ascorbic acid in the latter than in the controls. These results indicate that adrenal hypertrophy following a series of electroshocks represents an increased secretory function of the gland.

Effects of Electroshock on Adrenal Weights of Rats Treated with Anticonvulsant Agents.—It is shown in Table 5 that, although the adrenals of animals receiving nonconvulsant electroshock showed a significant increase in weight over those of untreated controls, the anticonvulsant drugs themselves caused a similar effect in

21. (*a*) Long.[13a] (*b*) Long, C. H. N., and Fry, E. G.: Effect of Epinephrine on Adrenal Cholesterol and Ascorbic Acid, Proc. Soc. Exper. Biol. & Med. **59**:67, 1945. (*c*) Sayers and Sayers.[13c]

nonshocked controls. In only one group were there clear-cut results to indicate that nonconvulsive electroshock can cause an increase in adrenal weight, and this was the group in which a preliminary shock served as the anticonvulsant agent to additional shocks which followed immediately.

Effects of Electroshock on Adrenalectomized Animals With and Without Intraocular Adrenal Transplants.—Of the three adrenalectomized animals without transplants, one died after the 4th shock; one, after the 5th shock, and the third, after the 12th shock. They barely survived each shock prior to their death, requiring continual artificial respiration, occasionally for as long as 10 minutes.

The three adrenalectomized animals bearing intraocular transplants of newborn-rat adrenals survived the 16-day course of daily electroshocks. None of them required artificial respiration at any time. Toward the end of the treatment period all began gaining weight, after a slight initial loss. One transplanted adrenal grew

TABLE 5.—*Comparison of Mean Adrenal Weights in Groups Receiving Anticonvulsant Agents, With or Without Electroshock*

Experimental Group	No.	Mean Adrenal Weight, Mg.	Mean Difference	t	P
Untreated controls	5	17.4	(3 vs. 8) 0.7	0.6	>0.50
DEP and shock	5	20.6	(4 vs. 5) 1.5	0.9	>0.05
DEP alone	5	22.1	.....	...	.....
Mephenesin and shock	5	23.8	(6 vs. 7) 1.8	0.9	>0.05
Mephenesin alone	5	22.0	.....	...	.....
Saline alone	7	18.1	(8 vs. 9) 2.5	2.2	0.03
Saline and shock	5	20.6	.....	...	.....
Shock 10 × daily (pretreated)	7	22.2	(10 vs. 11) 7.7	3.7	<0.01
Shock 1 × daily (pretreated)	7	24.5	.....	...	.....

at a rate of a similar preparation not being shocked; another transplanted adrenal grew at a slightly accelerated rate; the third grew at an extremely rapid rate, a rate of growth which had not previously been noted in any type of treatment, including administration of high doses of corticotropin. In addition to this accelerated rate of growth of the transplanted adrenal, the degree of maturation in the gland, manifested by the orange-yellow color, has rarely been seen in other transplants.

COMMENT AND CONCLUSIONS

The data of this experiment support the findings of Rosvold [10] and Novelli and Massini [12] that electroshock causes an increase in the adrenal weight of experimental animals. That this is probably a functional hypertrophy can be assumed, since there is a proportionately increased adrenal ascorbic acid content during the resting state 24 hours after shock. The finding that there is a sharp fall in adrenal ascorbic acid and cholesterol in the first few hours after a single electroshock offers still more evidence that the adrenal cortex is activated. These observations, together with the many clinical reports previously cited, lead to the conclusion that one effect of electroshock is to cause the release of endogenous corticotropin, since this hormone is the only substance known which can simultaneously effect adrenocortical secretion and hypertrophy.

The role of a convulsion per se in this process was investigated by attempting to administer nonconvulsive electroshock. Two methods were used to achieve this. The first method, that of premedication of animals with anticonvulsant drugs, proved successful in blocking a convulsion but, unfortunately, has given little information, since the drugs affect the size of the adrenal cortex and thus invalidate the use of hypertrophy as a measure of the effect of shock. Such a complication had been anticipated, and the utmost care was used in selecting the drugs used. Thus, curare and its derivatives were ruled out because of their well-known toxicity. Other anticonvulsants, such as the barbiturates, ether, and antiepileptics, like diphenylhydantoin (Dilantin), were ruled out because their site of action was too high in the central nervous system and previous reports have shown that this feature can partially or completely block the adrenocortical activation of electroshock.[22] The drugs chosen, mephenesin and DEP, were indicated, since they act primarily on the spinal cord and lower brain centers, are less toxic than curare, and have a very rapid, yet evanescent, action.[14] However, both proved unsatisfactory for the purposes of this experiment because of their independent effect on the adrenal. The use of anticonvulsant drugs in this type of study seems contraindicated until more satisfactory substances become available.

The other approach to nonconvulsive electroshock was more fruitful. This consisted of utilizing the all-or-none property of a convulsion [20] to block further convulsive response by administering electroshock during the tonic-extension phase. Thus, two groups of animals, both pretreated with a course of 10 shocks, were subjected to an additional course of 10 daily shocks; and in one group, while the animals were in the tonic-extension phase of a normal convulsive response, 10 further electroshocks were given rapidly over a five-second period, without in any way altering the typical convulsion. This group showed a significantly greater adrenal weight than the former, indicating that a convulsion is not necessary for at least some of the endocrine effects of electroshock. This technique, used for the first time in the present experiment, offers a valuable tool for future investigation.

Still another approach to the convulsion itself was seriously considered and then discarded after preliminary experimentation. This consisted of the use of so-called subconvulsive electroshock, which consists of administration of a current dose just below the threshold for a generalized muscular response, similar to the technique which has been used clinically on occasion.[19b] However, this approach was not feasible in rats, since they respond to administration of subthreshold current with intense hyperexcitability and running fits, which are in many ways more stressful than a convulsion itself. Furthermore, many authors have stated that the clinical effects of this type of electroshock are equivocal.[23]

The role of endogenous epinephrine in electroshock was studied to a limited degree with the use of an essentially demedullated preparation, the animal bearing an intraocular adrenal transplant. Evidence for the activation of the adrenocortical transplant by electroshock was observed. First, all the animals survived a 16-day course of daily shock, requiring no artificial respiration at any time and apparently adapting to the shock as normal animals. Second, a marked acceleration of the

22. Graham and Cleghorn.[19a] Rosvold, Kaplan, and Stevenson.[10]

23. Kalinowsky, L. B., and Hoch, P. H.: Shock Treatments and Other Somatic Procedures in Psychiatry, New York, Grune & Stratton, Inc., 1946.

transplant growth with a degree of maturation, as shown by the orange-yellow color, that has not been seen previously, even with animals given high doses of corticotropin, suggested that the adrenal transplant was being actively stimulated in some way by the administration of electroshock. Although this unusually rapid growth did not occur in all the transplant preparations given shock, it is a finding of real interest.

That no adrenalectomized animals survived longer than 12 days of daily electroshock, and that all required prolonged artificial respiration after each treatment that was survived, seem to establish two phenomena: (1) Electroshock is a stress which can be lethal, and (2) the adrenal is necessary to protect against this stress. Because of the latter, and because electroshock is such an easily administered and well-standardized procedure, it is proposed that it will shortly assume a more important place as a stress used generally in studies on the adrenal cortex and adaptation.

To return to the question of how the adrenal cortex is stimulated to secrete and hypertrophy after electroshock administration, if we assume that corticotropin is the direct mediator of this effect, then the question becomes one of how the pituitary is stimulated during electroshock to produce its tropic hormones. There are at present three widely accepted modes of anterior pituitary activation: The first type of pituitary stimulation is that produced by epinephrine, as described by Long.[13a,b] The exact manner in which this hormone of the adrenal medulla acts on the anterior pituitary is unknown, but it may be a direct action,[24] or may be due to more nonspecific effects.[21b] That epinephrine is the mediator, or at least one of the mediators, through which many varied stresses act to cause increased corticotropin production and adrenocortical activity has become widely acknowledged.

The second mechanism of pituitary activation is the so-called metabolic pathway. There is much evidence that the hypophysis secretes more corticotropin into the blood during adrenocortical insufficiency and suppresses corticotropin production in the presence of excess cortical hormones (summarized by Ingle [25] and Sayers [26]), but whether this is a direct effect of the target hormones, or is due to their metabolic consequences, is not definitely known.

The third mechanism, which has only recently become recognized, is the control exerted by the hypothalamus over the anterior pituitary. The work of de Groot and Harris [27] and Fortier and Selye,[28] as well as others, would seem to indicate that certain nuclei in the hypothalamus have a directing influence over anterior pituitary secretion. There is still uncertainty as to the actual method by which this control is

24. McDermott, W. V.; Fry, E. G.; Brobeck, J. R., and Long, C. H. N.: Mechanism of Control of Adrenocorticotrophic Hormone, Yale J. Biol. & Med. **23**:52, 1950.

25. Ingle, D. J.: Functional Interrelationship of the Anterior Pituitary and the Adrenal Cortex, Ann. Int. Med. **35**:652, 1951.

26. Sayers, G.: Regulation of Pituitary Adrenocorticotrophic Activity, in Adrenal Cortex: Transactions of the Second Conference, edited by Ralli, E. P., New York, Josiah Macy Jr. Foundation, 1949, p. 48.

27. de Groot, J., and Harris, G. W.: Hypothalamic Control of the Anterior Pituitary Gland and Blood Lymphocytes, J. Physiol. **111**:335, 1949.

28. Fortier, C., and Selye, H.: Adrenocorticotrophic Effect of Stress After Severance of the Hypothalamo-Hypophyseal Pathways, Am. J. Physiol. **159**:433, 1950.

achieved, but the concept that it is a neurohumoral mechanism, mediated by some sort of hypothalamic hormone, is gaining ground, and evidence for this theory is presented in the aforementioned papers.

It seems most likely that all three of the above mechanisms play a role in electroshock. There is every reason to suspect that large amounts of epinephrine are endogenously released during electroshock in human beings or normal laboratory animals, and Gellhorn and co-workers [29] have established that this is true in the latter. As yet there is no definitive evidence that the adrenocortical stimulation following electroshock can also take place in the absence of epinephrine, but the work reported here with animals bearing intraocular adrenocortical transplants, and thus essentially adrenodemedullated, would tend to indicate that epinephrine may not be essential for the endocrine effects following electroshock.

That muscular activity is a form of stress involving utilization of adrenocortical hormones seems well established, and, in fact, Ingle and associates [30] used the muscle-work test as a means of assay of cortical extract. Thus, it seems permissible to assume that there is an increased utilization of corticosteroids by the body as a whole during a convulsion, and thus some stimulus to the pituitary via the second mechanism mentioned, the metabolic pathway. That this is the primary, or only, mechanism would not tend to be substantiated by the work presented here, demonstrating that a convulsion is not necessary for all the adrenocortical hypertrophy of electroshock. Also, it has been shown elsewhere [10] that the fall in blood eosinophiles and other changes suggestive of adrenocortical activity can follow subconvulsive electroshock in human beings. However, it must be remembered that factors other than a convulsion can cause increased peripheral corticosteroid uptake during electroshock, and therefore the metabolic pathway cannot be completely discounted at this time.

Of all three types of pituitary stimulation, the hypothalamic probably plays the most important role in this stress. Lorimer and associates [31] have shown that during electroshock the current passes along the main neuronal pathways, rather than in an arc between electrodes, and they conclude that the current reaches structures deep in the brain and brain stem to a significant degree. Until measurements are made specifically within the hypothalamus for the amount of current reaching it during electroshock, one cannot say with certainty that there is direct electrical stimulation; but such an assumption seems most likely. Once this is established, the next step showing that such stimulation influences the anterior pituitary directly will readily follow, since it has been already demonstrated in rabbits.[27]

That the hypothalamus is involved in electroshock is indicated by various experiments. The changes noted in temperature control and activity,[32] appetite and

29. Gellhorn, E., and Kessler, M.: Effect of Electrically Induced Convulsions on the Vago-Insulin and Sympatho-Adrenal System, Proc. Soc. Exper. Biol. & Med. **46**:64, 1941. Gellhorn, E., and Safford, H.: Influence of Repeated Anoxia, Electroshock, and Insulin Hypoglycemia on the Reactivity of the Sympatho-Adrenal System, ibid. **68**:74, 1948.

30. Ingle, D. J.; Nezamis, J. E., and Morley, E. H.: Comparative Value of Cortisone, 17-Hydroxycortisone and Adrenal Cortex Extract Given by Continuous Intravenous Injection in Sustaining the Ability of the Adrenalectomized Rat to Work, Endocrinology **50**:1, 1952.

31. Lorimer, F. M.; Segall, M. M., and Stein, S. N.: The Path of Current Distribution in the Brain During Electro-Convulsive Therapy, Electroencephalog. & Clin. Neurophysiol. **1**:343, 1949.

32. Hoyt, R., and Rosvold, H. E.: Effects of Electroconvulsive Shock on Body Temperature of the Rat, Proc. Soc. Exper. Biol. & Med. **78**:582, 1951.

body weight,[33] and autonomic activity,[29] all implicate various hypothalamic nuclei. In addition, the fact that pituitary stimulation is not marked when electroshock is preceded by barbiturate medication,[22] the latter having a known depressant effect on the hypothalamus,[34] is another suggestive clue. The work reported here with animals bearing adrenal transplants and those receiving multiple electroshocks during one convulsion would also tend to emphasize the hypothalamic mechanism, since the results suggest that neither the sympathetic nor the metabolic pathways may be essential.

However, although it seems most likely that the hypothalamus does play the dominant role in directing the endocrine effects of electroshock, the proof of this is by no means established. Until such time as it is, the best approach is probably to consider that all three mechanisms, hypothalamic, sympathetic, and metabolic, are acting together to produce a pituitary-adrenal response of marked proportions.

SUMMARY

A significant increase in adrenal weight, from 20 to 40%, has been observed in male albino rats after chronic electroshock administration.

During the hours immediately following a single electroshock, a depletion of adrenal ascorbic acid and cholesterol has been noted.

Twenty-four hours after the 10th, and final, electroshock in another group of animals, an increase in the total ascorbic acid content, proportionate to the increase in weight, of the hypertrophied adrenals was found. This suggests a functional hypertrophy.

Animals receiving the anticonvulsant drugs mephenesin and DEP (diethylpropanediol) did not have a convulsion following electroshock administration, and their adrenals were enlarged. However, animals receiving the drugs alone also showed a significant adrenal hypertrophy.

Animals which were rapidly given 10 nonconvulsive electroshocks while in the tonic-extension phase of a previously administered electrogenic convulsion showed a significant adrenal hypertrophy, above that of controls receiving only one electroshock.

No adrenalectomized animals survived longer than a 12-day course of daily electroshocks, and each required continual artificial respiration after each shock, prior to death.

Adrenalectomized animals bearing intraocular transplants of newborn-rat adrenal survived a 16-day course of daily electroshocks and required no artificial respiration. A very rapid growth and maturation were noted in one of these transplants.

A discussion of these observations, as well as the possible mechanisms by which electroshock exerts its endocrine effects, is presented.

Dr. Royce's present address is State University of New York College of Medicine at New York City, Brooklyn.

33. Jensen, G. D., and Stainbrook, E.: Effects of Electrogenic Convulsions on the Estrus Cycle and the Weight of Rats, J. Comp. & Physiol. Psychol. **42**:502, 1949.

34. Leiter, L., and Grinker, R. R.: Role of the Hypothalamus in Regulation of Blood Pressure: Experimental Studies, with Observations on Respiration, Arch. Neurol. & Psychiat. **31**:54, 1934. Masserman, J. H.: Effects of Sodium Amytal and Other Drugs on the Reactivity of the Hypothalamus of the Cat, ibid. **37**:617, 1937.

Society Transactions

CHICAGO NEUROLOGICAL SOCIETY

Harold C. Voris, M.D., *President*

Leo A. Kaplan, M.D., *Secretary*

Regular Meeting, May 12, 1953

Acute Demyelinating Leucoencephalopathy. DR. JOSEPH A. LUHAN and DR. HAROLD MANFREDI (by invitation).

This communication deals with a case of acute demyelinating disease of rare incidence, diagnosed at its onset as a schizophrenic reaction.

The patient, a 28-year-old woman, had undergone change in personality of a schizoid nature for one year prior to admission to a psychiatric unit. Her disturbance had culminated in an acute psychotic reaction, marked by hallucinatory phenomena and negativistic behavior. Neurological examination on admission revealed no abnormality. During the second electroconvulsive treatment, the left extremities moved more weakly than the right, and thereafter rapid evolution of a decerebrate state with akinetic mutism occurred.

Repeated spinal punctures revealed mild pleocytosis, slight increase in protein, and a normal amount of sugar in the spinal fluid. Virus identification studies on the blood and spinal fluid gave negative results. The electroencephalogram revealed a very slow record.

The patient died 11 weeks after onset of the acute psychotic reaction, and necropsy revealed diffuse subcortical leucoencephalopathy with tendency to dissemination and concentric demyelination, limited to the two cerebral hemispheres. Microscopic sections revealed varying grades of demyelination, through severe demyelination with loss of axis-cylinders and formation of a delicate fibrillary glial lacework, containing numerous gemistocytic astrocytes, to areas resembling frank anemic softening. Infiltrative inflammatory reaction was absent throughout the neuraxis.

On the basis of morphological lesions, this case was classified as one of acute diffuse sclerosis, of an unusually devastating nature, without mesenchymal-hematogenous infiltrations, connoting a degenerative, noninfectious origin. Clinically, this case emphasized Bouman's contention that pronounced and early psychic symptoms are characteristic of acute diffuse sclerosis.

DISCUSSION

DR. RICHARD RICHTER: In the case I reported some years ago the demyelination was limited to the white matter of the hemisphere, while the other changes were in the pons and vascular area. I should hesitate to classify my early case, or Dr. Luhan's case, as one of diffuse sclerosis, for the demyelination is not diffuse, but clearly patchy. Just where the condition belongs in the demyelinating diseases one cannot say. Perhaps it might be classified as a disseminated myelitis.

I question the use of the term anemic softening, because it carries the implications that these areas of degeneration are infarcts.

DR. JOSEPH A. LUHAN: The various classifications of the demyelinating diseases carry inherent contradictions. For example, Pette, in his classification, speaks of diffuse encephalomyelitis as represented by diffuse sclerosis and postexanthematous encephalitis, in contradistinction to disseminated encephalomyelitis, under which he includes acute disseminated encephalomyelitis and ordinary chronic multiple sclerosis.

Ferraro has shown that a little of any of these components can be present in a disease having major characteristics that would entitle it to be classified as diffuse sclerosis. Thus, there are cases of diffuse sclerosis in which the pathologic picture fits the ordinary accepted pattern and

still shows widely scattered small lesions, as in multiple sclerosis. Hence, none of the present classifications seem entirely satisfactory, especially when the etiology and pathogenesis remain to be clarified.

I doubt whether one can draw many etiologic inferences from the pathologic lesions. As to the term anemic softening, I think Dr. Richter's criticism is well taken. We meant that the picture in this case is like that which we are accustomed to see in instances of anemic softening. Dr. Hassin had a favorite term for this—degenerative softening. But Dr. Hassin contradicted himself in various contributions of his concerned with certain acute demyelinating diseases, calling some of them acute disseminated encephalomyelitis and others, histologically quite similar, multiple degenerative softening.

The Betratron and Its Application to Therapy in Brain Tumors. Dr. A. Arnold, Dr. Percival Bailey, Dr. R. Harvey, Dr. L. Haas, and Dr. J. Laughlin.

The primary purpose of this paper was to demonstrate some of the physical aspects of high-energy x-rays as produced by the betatron which appear to be advantageous in the treatment of brain tumors. From a physical standpoint, the betatron is a source of high-energy x-rays. The University of Illinois medical betatron produces x-rays with an energy of 23,000,000 electron volts (23 mev), which is about 100 times that of conventional x-ray machines, with 200,000 to 400,000 electron volts (200 to 400 kev). As a result of such high energy, the x-ray beam from the betatron is more penetrating and has very little significant side-scatter. The dose distribution curve of high-energy x-rays is such that minimal absorption occurs on the surface and maximal absorption occurs at a 4-cm. depth in tissue. Because of these physical features alone, the therapist can deliver well-localized, uniform tumor doses with a minimal amount of irradiation to the healthy cerebral structures; furthermore, he can avoid irradiation of the more radioresponsive components of the brain, such as the brain stem and hypothalamus. The skin reactions with high-energy x-rays are insignificant.

(Isodose charts of patients treated, demonstrating these advantages, were shown.) The most striking delayed reactions observed in animals were the breakdown of the white matter in the cerebral hemisphere, cellular damage in the hypothalamus, and cellular and white matter changes in the brain stem.

DISCUSSION

Dr. Paul Bucy: I should like to ask Dr. Arnold whether he feels he can compare the results of betatron therapy, in which he used multiple portals, with standard x-ray therapy, in which he used only three portals. Certainly, if he were to use more portals with standard x-ray therapy, the damage to numerous parts of the brain would be reduced.

I should like to call particular attention to Dr. Arnold's statement that the breakdown of white matter occurred in his animals prior to the development of vascular lesions. This observation is completely at variance with the previous opinions held regarding the effect of the x-rays upon the nervous system.

Dr. Roland P. Mackay: May I ask Dr. Arnold what he thinks, in view of his experience, is the clinical applicability of betatron irradiation in cases of brain tumor? It would appear that therapeutically effective doses closely approach those which destroy normal tissue, with the result that little profit would accrue from the use of betatron radiation in such cases.

Dr. Harold C. Voris: The depilating effect of x-rays is of relatively secondary importance, but it is important psychologically to the patient, and often to the patient's family. I gather from what Dr. Arnold said, and from the photographs, that there is a depilating effect, but I should like to ask whether there is a later return of hair.

Dr. A. Arnold: In answer to Dr. Voris: Using sufficient cross-fire technique, we have been able to irradiate a small tumor, like a pituitary tumor, to a much higher degree than with the standard x-ray method and not lose a single hair. When epilation and skin effects occurred, they were very mild and short-lived and recovery was complete; so we do not expect any development of lesions or breakdown of the skin.

The intolerance of the nervous system for radiation is such that we are limiting the total dose that we give to tumors of the brain stem; the brain stem will not tolerate over 5,000 r.

Presidential Address: The Skull. Harold C. Voris.

NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY AND THE NEW YORK NEUROLOGICAL SOCIETY

Louis Hausman, M.D., *Chairman, Section of Neurology and Psychiatry, Presiding*

Joint Meeting, Feb. 10, 1953

Frontal Lobe Syndrome in Thrombosis of the Internal Carotid Artery. DR. JUAN NEGRIN JR.

Spontaneous thrombosis of the internal carotid artery in the neck is a somewhat uncommon condition. The clinical diagnosis of such a lesion has been the subject of a great deal of discussion and disagreement.

During the last few years I have used cerebral angiography either by the open or by the closed method when indicated. In the course of such experience, a positive diagnosis of spontaneous thrombosis of the internal carotid artery was made in nine patients, all of whom I saw at one time or another during their illness. A superficial analysis of the clinical findings seemed to indicate that these patients had a syndrome referable to the frontal lobe, with other symptoms, not always present, secondary to involvement at times of nearby structures. It was considered of interest to study these patients in order to determine what neurological characteristics they might have in common and to emphasize once more that this pathologic process is one of those that may produce hemiplegia. Since it is no doubt also one of the causes of "apoplexy," its early recognition will result in diagnosis and adequate treatment of the patient. In order properly to understand the symptomatology of the lesion presented, one should be aware of the distribution and anastomosis of the arteriovenous system of the frontal lobe, as well as the anastomosis between the external and the internal carotid artery.

The neurological picture will depend on the collateral circulation, mainly through the circle of Willis. It will also be modified by the distribution of the cerebral blood vessels, which has many normal variants. Besides, the thrombosis may extend to a greater or shorter distance cephalad, with subsequent partial or total direct interruption of the blood flow into more terminal branches. If this extension is too severe, a fatality may occur. All these possibilities are the reason for the varied symptomatology secondary to ischemia of one cerebral hemisphere. However, it was possible to see that all our patients presented in common a frontal lobe syndrome, characterized by the presence of hemiplegia, very often a mental picture characteristic of frontal lobe involvement, and aphasia whenever the dominant side was affected.

In these patients the course of the disease had a chronic prodromal stage, the duration varying from a few days to a few years. After this chronic period, or in the absence of it, the phase appears which may or may not be accompanied by loss of consciousness. The acute attack produced signs referable to the homologous cerebral hemisphere, frontal lobe signs developing in a step-like fashion, with hemiplegia and aphasia, mental symptoms, and, more rarely, symptoms not derived from the frontal lobe, such as hemianesthesia, hemianopsia, and blindness.

If the condition became stabilized, the patient survived, with little tendency to neurological improvement. Roentgenograms of the skull, lumbar puncture, an electroencephalogram, or air studies showed no specific abnormalities. A definite diagnosis can be obtained by cerebral angiography when one or all of the following specific signs are observed:

1. The contrast medium is arrested at or shortly above the bifurcation and fills the common and external carotid arteries.

2. The contrast material is halted at the level of the obstruction in the internal carotid artery and may pass in retrograde fashion down the common carotid artery and over to the opposite common carotid system, including the external and internal carotid arteries.

3. The anterior and the middle cerebral artery or both on the involved side fail to fill.

DISCUSSION

DR. LESTER A. MOUNT: It is important to emphasize that the clinical findings are variable and depend both on the extent of the thrombosis and on the degree of collateral circulation, as well as the presence or absence of arteriospasm. We have had two cases in which thrombosis of the internal carotid artery, or perhaps a congenital absence of the internal carotid artery,

was mistaken in the arteriogram for another condition—in one case an aneurysm of the internal carotid artery, and in the other a tumor of the brain. In the arteriogram one must differentiate between arterial spasm and thrombosis. I have had a few cases in which one injection seemed to demonstrate thrombosis of the internal carotid artery, but another injection on the same day showed good filling of the internal carotid artery. I believe this is due to arterial spasm.

Another interesting point is that the arteriographic procedure may result in an increase in the patient's symptoms, even if there is complete thrombosis of the internal carotid artery and none of the contrast material enters the brain. This, also, I believe to be due to arteriospasm.

DR. HERBERT PARSONS: As the cases of thrombosis of the internal carotid artery accumulate, it becomes evident that the condition is much commoner than was originally suspected. Most of the early cases were encountered fortuitously when arteriographic studies were done on patients suspected of having intracranial tumors, aneurysms, or vascular anomalies. In retrospect, when one reviews the case histories of these patients, one realizes that thrombosis of the internal carotid artery should have been suspected from the beginning.

The most important clinical sign leading one to suspect the presence of thrombosis of the carotid artery is obtained by careful palpation of the artery in the neck.

DR. SAMUEL BROCK: May I say a word about the etiology of thrombosis of the internal carotid artery? The English report that it is not uncommon to find this condition on the basis of thromboangiitis obliterans in the younger age groups, without any manifestations of the disease in the extremities. This is really a form of cerebral involvement with particular implication of the internal carotid artery (Cloake, P. C. P.: Certain Vascular Diseases of the Nervous System, in Feiling, A.: Modern Trends in Neurology, Paul B. Hoeber, Inc., New York, 1951, Chap. 14, Pts. 2 and 3). Given a young person with this syndrome, one should think of thromboangiitis obliterans as a possible etiologic factor. This leads to another recommendation. When one encounters thrombosis of the internal carotid artery (proved by arteriography or other means), one should ask the surgeon to get a piece of the occluded artery for histologic review. Do not be surprised to learn that thromboangiitis obliterans is the basic disease in a certain percentage of cases.

DR. HENRY S. DUNNING: The only place in which the pulsation of the internal carotid artery can be isolated is in the pharnyx. Externally in the neck, this artery lies so close to the external carotid artery that their respective pulsations cannot be differentiated. In the pharynx the internal carotid artery lies in the lateral wall behind the pharyngopalatine muscle, and any pulsation felt there is due exclusively to this artery. In persons who are able to inhibit the gag reflex, and it is surprising how many can do so with gentleness of palpation and encouragement, it is easy to feel the pulsation. If none is felt, it is concluded that the lumen of the artery is very narrow or nonexistent.

I agree with Dr. Parsons that arteriosclerotic occlusion of the internal carotid artery is rather common. Since March 5, 1952, a period of 11 months, I have been palpating in the pharynx for pulsation of this artery in all patients having suggestive cerebral or visual symptoms and have found five cases of occlusion, in each of which the thrombosis was the obvious cause of the symptoms. In three cases the occlusion was unilateral, and in two, bilateral.

As compared with carotid arteriography, pharyngeal palpation is simple, safe, and inexpensive and should become a widely used method for the detection of occlusion of the internal carotid artery.

DR. I. S. WECHSLER: Occlusion of the internal carotid artery abolishes the function of practically the whole hemisphere with the exception of the occipital region. I do not know what Dr. Negrin means by frontal-lobe syndrome in occlusion of the internal carotid artery. It is masked by signs and symptoms of involvement of the parietal and temporal lobes. In the acute cases there is practically no opportunity for collateral circulation, and most of the patients die. Generally the diagnosis is made accidentally.

Dr. Dunning's method of palpating the internal carotid artery in the pharynx is excellent but requires skill which neurologists do not have, but I suppose they could learn. Frankly, I wonder how one can do more than suspect an occlusion.

DR. LOUIS HAUSMAN: Dr. Negrin, how many of the patients gave evidence of peripheral vascular disease in other parts of the body?

DR. JUAN NEGRIN JR.: Dr. Hausman's question is related to Dr. Brock's concerning thromboangiitis obliterans as the cause of thrombosis of the internal carotid artery. None of our patients had well-defined evidence of peripheral vascular disease, except that some had moderate arteriosclerosis but no definite impairment of peripheral vessels. None of our cases, I believe, could be considered in the group of thromboangiitis obliterans. Dr. Lewis Stevenson's histologic report on the thrombus in the internal carotid arteries of the two patients who died made no mention of thromboangiitis obliterans.

In reply to Dr. Mount's question regarding arterial spasm: None of our patients had any arterial spasm. This diagnosis was properly eliminated not only by angiography on the normal and on the affected side, but in seven cases by direct exploration. To avoid producing an increase in the patient's symptoms after angiography, one may sometimes accept the roentgenographic findings from the injection on the normal side as sufficient confirmatory and diagnostic evidence.

Dr. Parsons's comment on the occasional hemianopsia observed leads me to remark that perhaps this defect is due to an extension of the thrombosis to the anterior choroidal artery and ischemia or necrosis of the geniculostriate projection pathway supplied by this artery.

I believe that the use of anticoagulants in the early stages of this condition would be a good idea.

In response to Dr. Wechsler's question about the frontal lobe syndrome, it is interesting to emphasize that the only symptoms common to all these patients were referable to the frontal lobe: hemiplegia or hemiparesis, aphasia when the dominant side was involved, and a mental syndrome indicative of a frontal lobe disorder.

Amino Acid Chromatography of Neural Tissues and Fluids. DR. PINCKNEY J. HARMAN (by invitation).

Two-dimensional paper chromatography provides a relatively simple technique for qualitative and semiquantitative analysis of tissues for many substances of biological interest. Amino acids present in neural tissues and fluids may be separated in two dimensions on filter paper using phenol water and lutidine-ethanol water as the two solvents and a ninhydrin spray for visualization.

Neural tissues and fluids of similar histology appear to have a consistent normal pattern of free amino acids. These amino acids are apparently interrelated biochemically and are subject to modification in pathologic states. Results indicate that amino acid chromatography is useful in investigating the metabolism of neural tissues and may find clinical use both in the detection of pathology and in the elucidation of the chemistry of neuropathology.

DISCUSSION

DR. MORTON NATHANSON: Dr. Harman should be commended on his work and the clear presentation of this relatively new method of approach. Every method opens avenues to new information, and paper chromatography as applied to the nervous system is indeed promising. The simplicity of the method is a great advantage. Many protein fractions and amino acids can be studied simultaneously, and relationships between the two ascertained within limits.

I should like to ask Dr. Harman several questions: Does he have any information on the chromatographic patterns of diseased nerve tissue in animals? How consistent are the patterns from the same animal or tissue at different times? In the past few years glutamic acid has been investigated for its possible effects on cerebral function. In the light of this, and the work presented here, do you think that the γ-aminobutyric acid that was found only in the gray matter could be the significant factor, rather than the glutamic acid?

DR. ARTHUR SHAPIRO (by invitation): Two fractions were described, of which one was bound to the protein and the other was not bound to the protein. In chemical terms, what precautions were taken to prevent partial breakdown? That is, were you dealing with amino acids that are free in the intercellular fluid, or with the first fraction, due to the breakdown of protein, possibly by intrinsic enzyme systems in the cells?

DR. LOUIS HAUSMAN: Will you tell us, Dr. Harman, how difficult this technique is to learn, and how difficult it would be to incorporate it in clinical studies?

Dr. Pinckney J. Harman: I shall start with Dr. Hausman's question. The technique can be learned by the average technician in about a week and can be carried out easily in the laboratory. However, it is important to have a chemist for consultation.

Dr. Shapiro asked about the free versus the combined protein. I meant to imply that bound within protein.

Dr. Nathanson asked about γ-aminobutyric acid versus glutamic acid. I have very little information on that. I made a few metabolic studies and found that an intravenous injection of γ-aminobutyric acid can alter the pattern of free amino acids.

There is a definite and consistent change in peripheral nerve undergoing degeneration, and this change is about the easiest finding of all to verify. It seems that during the proliferative phase of the sheath elements during degeneration of the nerve, all the free amino acids are greatly increased in concentration, and some are increased more than others.

Prognosis and a Method of Treatment of Multiple Sclerosis. Dr. Joseph Wilder (by invitation).

Statistical evaluation of data in the literature and observations in a new series of 140 of my own cases in which a new compound, Pancorphen, was used lead to the conclusion that the present nihilistic trend in the therapy of multiple sclerosis is not justified. Many treatments published achieve immediate results far beyond the average incidence of spontaneous remissions (one in 3.7 to 4.5 years).

We must concentrate, rather, on the problem of repeating and maintaining these therapeutic remissions. The average duration of a remission is much longer than that of the active periods. "Progressive remissions" deserve attention. A spontaneous remission in attacks may last as long as 17 years. These remissions occur not infrequently in attacks that have been progressive for over 10 years. The prognosis is poorest after about one year's duration, when it improves again.

Pancorphen consists of beef heart digested by hog pancreas, with phenol added for sterility and pharmacologic effect. The injections produce minimum systemic and outspoken focal neurological reactions. Prolonged vasodilatation, as well as spasmolytic effects, are typical. The improvements were achieved within four weeks and were considerable in 25%, moderate in 36%, slight in 23%, and absent in 16%. Relapses are common. Repetition of treatment yields mostly fresh improvement. The therapy can be applied in a few other conditions.

DISCUSSION

Dr. Richard M. Brickner: In confronting the problems of evaluation of a treatment of multiple sclerosis, Dr. Wilder has proceeded without prejudice, so to speak. He has not been floored by the difficulty inherent in the evaluation of spontaneous remissions, nor has he let himself be fooled by them. This state of objectivity is not something that can be attained by every physician, for spontaneous remissions do generate emotions in students of multiple sclerosis. I should like more detail about the manner in which improvement occurs. For instance, does it occur promptly after an injection? Do the symptoms return between injections, assuming that they do show improvement? I have some questions concerning the vasodilating effects of Pancorphen. Is there any evidence of an effect on the intracranial blood vessels, or is the action all peripheral? Again, does improvement occur in relation to the appearance or cessation of flushes?

Dr. Alexandra Adler: Dr. Wilder's painstaking experiments and observations on the treatment of multiple sclerosis have been going on for more than 20 years. It is from such extensive observations that we gain most information on the course and prognosis in chronic diseases, such as multiple sclerosis.

Dr. Wilder was kind enough to let me see two of his patients who had been ill for many years. They had been treated with repeated injections. The patients concurred in their praise of the effect of the injections. There is no doubt as to their objective improvement, which really seems lasting, and not merely transient, as was preponderant in Dr. Wilder's description of his cases.

DR. JOSEPH WILDER: In answer to some of the questions raised by Dr. Brickner: Only remissions following immediately the last of the five injections were attributed to the treatment. He asked whether I have evidence of intracranial vascular dilatation. I think he has such evidence; inhalation of amyl nitrite raises the spinal fluid pressure very promptly. My proofs are not of that kind, but I have succeeded in a number of cases in stopping the beginning of a migraine attack or in producing dilatation of the vessels of the eyegrounds. It is true that this is more or less parallel to the flush.

Hepatolenticular Degeneration (Wilson's Disease): A Family Study. DR. FRANK SULLIVAN, DR. HERBERT L. MARTIN, and DR. FLETCHER MCDOWELL (all by invitation).

A family of seven children of which five, including one pair of twins, have had progressive hepatolenticular degeneration, was presented. The study was unusual in that a survey of the literature revealed only one family with a larger number of members afflicted and only two patients living as long with the disease as the two members presented. These two patients, still living 21 years after the onset of symptoms and presenting both clinical and biochemical evidence of the disorder, were reported on in the nature of a follow-up of a study made in 1931 by Dr. Frank J. Curran (*J. Neurol. & Psychopath.* **12**:320-328, 1932). The twins have been extensively studied; while they exhibit characteristic low serum copper concentration and low serum ceruloplasmin content, no such abnormality can be demonstrated in the unaffected mother and sister.

DISCUSSION

DR. ALEXANDER BEARN (by invitation): Although the disease is clearly familial, the very large number of siblings affected in this family is exceptional, at least in my experience. I believe that in the past we have been inclined to pay too much attention to the increased urinary excretion of copper. While this undoubtedly occurs, it is by no means specific. The mother of this family, now aged 64, does not exhibit any clinical evidence of Wilson's disease and, except for an increased urinary excretion of copper, does not have any of the typical biochemical abnormalities. If any one biochemical abnormality is to be chosen for diagnostic purposes, perhaps a low serum copper is at the moment the most helpful, and so far we have not encountered it in any other condition. If this low serum copper level is accompanied by a high urinary copper excretion and by an increased amino-aciduria, the diagnosis of hepatolenticular disease can be firmly established. I might add that in some cases of cirrhosis, particularly of the biliary type, an increased urinary excretion of copper exists, but in these cases the serum copper level is always raised and the differentiation from Wilson's disease can be clearly drawn.

Richard M. Brickner, M.D., President, New York Neurological Society, Presiding
Louis Hausman, M.D., Chairman, Section of Neurology and Psychiatry, Presiding
Joint Meeting, March 10, 1953

PANEL DISCUSSION ON NONPSYCHOGENIC ORIGINS OF PSYCHOSES.

I. Role of Adrenal Cortex in the Origin of the Psychoses. DR. HUDSON HOAGLAND (by invitation), Shrewsbury, Mass.

A group of us at the Worcester Foundation for Experimental Biology and the Worcester State Hospital have studied the adrenocortical physiology of male schizophrenic patients over the past 10 years. We have found that, on the average, under resting and fasting conditions and also under conditions of stress the patients' urinary excretion patterns, reflecting adrenocortical function, display differences from those found in normal men of the same age range.

Thus, in a study of 72 normal men and 67 schizophrenic patients we found that at rest the patients excrete more 17-ketosteroids, less total adrenocortical hormone, much more sodium, somewhat more potassium, and much less inorganic phosphate than do normal men. Excretion of uric acid is the same in the two groups. These differences are all statistically significant. The patients excrete more than the normal percentage of β-ketosteroids and considerably less than normal nonketonic steroid. Chromatography of urinary steroids has demonstrated 35 sub-

stances, 29 of which are present in all normal urines. While chromatographic studies have been made on relatively few patients and normal subjects, preliminary evidence indicates suggestive differences of patterns of specific steroid excretion in the two groups.

After three standardized stress tests and the injection of 25-mg. test doses of corticotropin, the patients were found to show considerably less adrenal response on the average than did the normal subjects. Under these test conditions percentage increases in urinary 17-ketosteroids, uric acid, sodium, and potassium were considerably less in the patients. On the other hand, the patients displayed a markedly increased output of phosphates, not seen in the normals. No differences in percentage changes in adrenocortical hormones, lymphocytes, or eosinophiles were found to differentiate normal and schizophrenic groups. Similar differences in adrenal responsivity to stress and to corticotropin have been confirmed by two independent groups of investigators. There is evidence of abnormal adrenal responsivity in other forms of psychosis.

Our findings do not prove that the adrenal abnormalities cause the psychosis—they may be a result of it. It is, however, known that psychosis may accompany hyperplasia of the adrenal gland and may result from massive, repeated doses of corticotropin and cortisone in persons hitherto nonpsychotic. Studies under way of bilaterally adrenalectomized schizophrenic patients maintained on cortisone and on other forms of replacement substances should shed light on the relation of the steroid abnormalities to psychosis.

II. Evidences from Studies of Childhood Schizophrenia. Dr. Lauretta Bender

The present definition of childhood schizophrenia is that of a maturational lag at the embryonic level in the biological processes underlying organismic behavior with an embryonic plasticity characterizing the disordered behavior in every area. Etiologic factors are heredity and a precipitating physiological crisis, which may be birth.

The diagnosis was made at Bellevue Hospital for 626 children, aged 2½ to 12 years, between 1934 and 1951, inclusive. It was confirmed from 5 to 15 years later, in 1950-1951, in 89% of 143 cases in which it was made between 1938 and 1946. The patients were then 11 to 28 years old. Thus, schizophrenic children become schizophrenic adolescents and adults. Forty per cent of these had one parent known or suspected to be schizophrenic. We have observed characteristic (plastic) disturbances in behavior in all those areas outlined by Gesell (Embryology of Behavior, New York, Harper & Brothers, 1945), i. e., (1) homeostasis, with psychosomatic disorders; (2) respiratory patterns, with disorders in associated functions of speech, language, and thought; (3) sleep and waking patterns, with disturbances in states of consciousness; (4) muscular tone; (5) tonic-neck-reflex attitudes (disturbances in postural reflexes and whirling motility).

Statistical analysis of diagnostic criteria shows that those derived from the above dysfunction, and nearest the biological core of the organism, are most significant in the differential diagnosis of childhood schizophrenia and psychogenic behavior disorders.

Maturation of schizophrenic children in the first three years of life deviates from Gesell norms with a variable unevenness, with the common feature of an embryonic lag and plasticity, starting from birth. In contrast to the findings of Leo Kanner that the young autistic child comes only from the homes of cold, "refrigerator," oversophisticated, overeducated parents, we found, when we reviewed the background of 90 schizophrenic children, aged 2½ to 6, that every type of home was represented, least often the oversophisticated, oftenest intact (both parents, interested, or overinterested), middle-class homes with a strong (over 40%) family history of schizophrenia. Some homes were of the very worst, while some infants had been placed in early substitute homes, having been abandoned or removed from psychotic parents.

III. Pavlov's Experimental Work and Psychoses. Dr. Joseph Wortis (by invitation)

It is not widely enough known that Pavlov, in the last decade of his life, turned his interest to problems of clinical psychiatry. Starting from his observations on the peculiarities of response encountered in dogs in various stages of deepening inhibition, he concluded that the symptomatology of schizophrenia corresponded to that of partial inhibition, and that schizophrenia was a condition of chronic hypnosis, due to a weakening of the cortical cells and to the compensatory protective inhibition. In addition to constitutional factors, he believed that toxins, infections, endocrine imbalance, life stresses, exposure to conflict, and the condition of the

organism could all contribute to this weakness. He regarded obsessions and paranoia as conditions in which a fixed focus of excitation was maintained on the cortex, surrounded by normal cortex in the case of obsessions and by inhibited cortex in the case of paranoia. He attached great importance to the therapeutic value of protective inhibition and encouraged the use of sleep treatment. He regarded the manic state as a reflection of labile explosive excitation, with an intense but brief response, corresponding to a condition of irritable weakness. His classic demonstration of the experimental neurosis that develops when the organism is exposed to insoluble or very difficult problems of discrimination has wide implications for clinical psychiatry. It is unfortunate that so much important recent work by Pavlov's pupils is not being abstracted in our medical journals. We must agree with Pavlov, who said that psychiatrists "will inevitably have to reckon with these fundamental pathophysiological phenomena."

IV. Experimentally Produced Abnormal Mental States. DR. PAUL H. HOCH.

Experimentally produced abnormal mental states were discussed. The effects of mescaline and lysergic acid and the changes which these drugs produce in normal persons were described. Affectual, perceptual, and behavioral changes, as well as hallucinations, delusions, and depersonalization changes produced by these drugs in normal subjects were discussed.

The effects of mescaline and lysergic acid on schizophrenic patients were also reported. It was found that physiological changes were produced in these patients and that their mental symptoms were greatly aggravated. Mescaline and lysergic acid are drugs that disorganize the psychic integration of the individual. This disorganization is much more apparent in schizophrenic than in normal subjects. The relation of these investigations to the organic cause of schizophrenia was discussed. More detailed information can be obtained from the following articles: Hoch, Paul H.: Experimentally Produced Psychoses, *Am. J. Psychiat.* **107**:607, 1951. Hoch, Paul H.; Cattell, J. P., and Pennes, H. H.: Effect of Drugs: Theoretical Considerations from a Psychological Viewpoint, ibid. **108**:585, 1952; Effects of Mescaline and Lysergic Acid, ibid **108**:579, 1952. Hoch, Paul H.: Experimental Induction of Psychoses, in *Biological Aspects of Mental Health and Disease*, Milbank Memorial Fund, New York, Paul B. Hoeber, Inc., 1952; Evaluations of Newer Pharmacodynamic Therapies, Including the Narcoanalytic Use of Drugs, in Psychiatric Treatment, Baltimore, Williams & Wilkins Company, 1953, Vol. 31; Psychoses Produced by Administration of Drugs, in Metabolic and Toxic Diseases of the Nervous System, Baltimore, Williams & Wilkins Company, Vol. 32, to be published.

DISCUSSION

DR. LEONARD CAMMER: I would like to ask Dr. Hoagland whether any of his studies indicate that disturbances in adrenocortical activity influence cerebral metabolism. I wonder whether he would comment on his work with perfusion of the adrenal glands and the new information on the relation of substances in the perfusate to schizophrenia.

DR. HUDSON HOAGLAND: We have investigated the effects of adrenocortical hormones on cerebral metabolism and the electrical properties of the brains of rats. We found brain slices and homogenates to respire at the same rates whether taken from adrenalectomized or from normal rats. However, our in vivo studies indicate a decreased cerebral blood flow and a decreased oxygen consumption of the brain, with an accompanying slowing of the electroencephalogram, in salt-maintained rats after adrenalectomy. The blood flow, oxygen consumption, and electroencephalographic frequency are restored together by certain adrenal steroids, but not by others. We have also found conduction time from the foot to the somatic sensory cortex to be increased after adrenalectomy. The sciatic nerve shows decreased excitability in adrenalectomized rats. These factors may also be restored by the administration of suitable steroids. Thus, in the rat adrenocortical hormones do influence both metabolic and electrical properties of the nervous system.

Dr. Cammer asked about perfusion studies of adrenal glands at the Worcester Foundation. Dr. E. Romanoff has used techniques developed by our colleagues from their perfusion studies of beef adrenals to investigate steroidogenesis in human adrenals, especially after administration of corticotropin to the perfusing blood. Some 20 adrenals removed from patients with cancer, hypertension, or schizophrenia have thus been studied. Romanoff has chromatographically

demonstrated 30 to 40 substances, primarily of steroidal nature, in the perfusate after corticotropin administration. Pattern differences in excretion of these substances in relation to several diseases, including schizophrenia, are being studied and will be reported upon later.

DR. WALTER S. BOERNSTEIN: The experimental investigation of psychoses by the application of such drugs as mescaline and lysergic acid brings us closer to a solution of the problem of the relation of the symptomatology of the psychoses to the cerebral processes. Although the results of Dr. Hoch's research do not as yet warrant the formulation of definite assumptions, one ought, nonetheless, to raise the question as to which systems of the brain are predominantly involved in such abnormal states as have been discussed here. From this point of view, two circuits in the brain should be distinguished, viz., (1) the thalamocorticothalamic circuit, which subserves man's relationship to the outside world, and (2) the hypothalamocorticohypothalamic circuit which chiefly subserves the individual's relationship to his inner world.

In schizophrenic states the equilibrium between the individual's relations with the outside world and those with his inner world is disturbed in favor of the latter. It is hypothesized that in these states the hypothalamocorticohypothalamic circuit becomes functionally predominant. Experiments which I began years ago, but had to abandon prematurely, would tend to justify this hypothesis. In this connection, one would do well to consider the theoretically important "uncinate state," with its hallucinations in dream-like conditions (preliminary report in Proceedings Rudolf Virchow Medical Society, 1950; Proceedings of Thirteenth International Psychological Congress, Stockholm, 1951).

PHILADELPHIA NEUROLOGICAL SOCIETY; NEW YORK NEUROLOGICAL SOCIETY, AND NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY

E. Jefferson Browder, M.D., *Vice-President, New York Neurological Society, Presiding*

Joint Meeting, April 17, 1953

Cataplexy Precipitated by Acute Aggressive Impulses. DR. MAX LEVIN, New York.

Cataplexy is oftenest precipitated by laughter. It may occur also when the patient is about to give expression to an aggressive impulse that arouses guilt, as when an angry father raises his hand to strike his child. Because the angry father is also, consciously or unconsciously, ashamed and guilty, there is conditioned inhibition, which may become overt as cataplexy. Cataplexy may also occur when the patient is on the point of expressing his aggression in the course of such sport as hunting and fishing, and even in sport in which the aggression is purely symbolic, as in baseball, tennis, and chess.

A fuller presentation of this paper appeared in the February 1953 issue of the ARCHIVES, page 224, under the title "Aggression, Guilt, and Cataplexy."

DISCUSSION

DR. ROBERT L. LEOPOLD, Philadelphia: Dr. Levin is to be congratulated on his repeated investigations of this interesting subject and on bringing this little-understood phenomenon to our attention.

It would appear that we are attempting to delineate the relation between two groups of variable factors. The first of these is the problem of narcolepsy itself, in particular, of that subdivision of narcolepsy called cataplexy. Kinnier Wilson, in reviewing the subject, stated that in a considerable minority of cases the cataplexy may be due to previous encephalitic involvement, and in a small minority of cases, to arteriosclerosis, cerebral tumors, and other lesions, but that in a great many cases the cause is unknown. The neurophysiologic or electroencephalitic data concerning the actual electrical disturbances which occur during the course of a cataplectic seizure are relatively few.

There can be no doubt that cases of cataplexy with structural changes represent physiologic responses, and not psychological conditions. In cases in which the cataplexy is without structural changes but is accompanied by narcolepsy, it is better to think in terms of a physiologic condition, and not primarily in terms of a psychological disturbance. There are undoubtedly cases in which the cataplexy is primarily due to psychological disturbances. In these cases

aggression accompanied by guilt may be the trigger mechanism, but even in these cases other symptoms of character disorder should be elicited before a primary diagnosis of psychological illness is made.

Selected Intracranial Cerebral Electroshock Therapy. Dr. Juan Negrin Jr., New York.

There are many failures with electric shock therapy when given alone or combined with pharmacological shock. The specific indications for a particular psychosurgical technique are not yet clearly defined, and the results cannot be predicted. We have not had at our disposal a method for the treatment of psychosis which is, with respect to its radical nature, between the electric shock and the usual psychosurgical procedures.

Several years ago I thought that the administration of electric shock to the brain by way of intracranially placed electrodes would permit an improvement in the therapeutic results of electric shock because of its more selective application and its direct action to specific cerebral regions. Although this type of electric shock is more radical than the external electric shock, it does not produce the extensive irreversible anatomical changes of the psychosurgical techniques commonly employed. Prior to 1947 I used several types of experimental electrodes. In 1948 electrodes were built according to specifications, with the cooperation of Medcraft, permitting the initiation of this project in treatment of humans. The elecrodes are placed in the selected brain areas through trephine openings, and the necessary shock treatments are administered.

(The author projected a moving picture of the technique, showing the electrode placements and the results of this type of treatment in a woman aged 53.)

The clinical application of this method is intended for those conditions that do not respond to the usual electric shock therapy, alone or combined with pharmacological shock. Since it does not result in the extensive irreversible anatomical changes produced by psychosurgery, it could, logically, be given a trial prior to resort to such surgical procedures.

DISCUSSION

Dr. Harvey Bartle Jr., Philadelphia: This is the most interesting technique, and it lies somewhere in the zone between lobotomy and ordinary electroshock therapy. This paper suggested three points for further consideration and investigation: Can we hope for better results with this method than with the ordinary electroshock technique? Can we hope for a more lasting recovery, for a higher percentage of improvement, or for results in chronic patients, as against those in acute patients only? If this technique does produce better results than the ordinary method, can it be accounted for by the fact that the current is passed through the brain? If so, perhaps a trial of giving only petit mal seizures should be made and the effect noted. Most of us agree that petit mal seizures do nothing for most patients. But would they if given by this method have a different effect than if given by the usual technique? This treatment might be applied to patients in whom no convulsion can be obtained with electric shock, such as those with a high threshold.

Dr. William W. Wilson, Philadelphia: There are a number of points concerning which I should like to ask Dr. Negrin, such as the number of milliamperes used and the voltages. I was most impressed by this film, and I believe the method should be tried out further. I heard someone from the front of the room ask whether this patient was given electric shock treatment before this method was tried, and I think the answer was "No." I wonder whether the same result would have been obtained by the external method in this particular case. I should like to ask Dr. Negrin what happens to the electrodes.

Dr. J. Lawrence Pool, New York: This paper, while the report of only one case, is of particular interest to me, especially because in 1948 I had a similar idea, as probably many of us have. Dr. Negrin gives me courage to report for the first time a somewhat similar effort along this line.

I thought then that it might be of interest to try the effects of specific, local shock therapy which might benefit a psychotic patient needing electric shock therapy, but in which a convulsive seizure would be avoided. This idea was based on the observation that a chronically mute schizophrenic patient, operated on with local anesthesia, responded with verbalization on stimulation of the anterior cingulate cortex. This suggested the idea of implanting a small secondary

induction coil permanently in the skull, with the electrodes applied to the anterior cingulate cortex. A primary induction coil outside the head could thus be used when necessary for localized shock therapy. In another case, one of Parkinsonism with depression, the electrodes were placed in the caudate nucleus with a view to inhibition of severe tremor. In the first case there was no specific effect, and it was subsequently found that one intracranial electrode was broken. In the second case there seemed to be definite amelioration of depression during and after stimulation of the caudate nucleus, but no effect on tremor or rigidity. Whether the effect was real or was due to suggestion, the patient requested the treatment every day. Of these two cases, the electrodes are still in place in one and have been removed in the other. Local scarring of the brain was noted where the electrodes had been. There were no other adverse effects of the coil-electrode implantation.

Dr. Lothar B. Kalinowsky, New York: Dr. Negrin has presented an ingenious technique, the place of which is not yet entirely clear. We all hope for something which is between electric shock treatment and psychosurgery; I am afraid, however, that this method is actually a type of electric shock treatment, applied after a surgical procedure which only opens the skull and has no therapeutic effect in itself. The essential point of attack, therefore, remains current itself. Whether the electric current is applied directly to the cortex or to the unopened skull does not, in my opinion, make any great difference. Focal application of the current in different areas of the cortex, which this technique facilitates and undoubtedly will stimulate, has been tried, without changing the therapeutic results, which depend on the convulsions rather than on the current or its site of application. I therefore do not see that the new technique offers a treatment between electric shock and psychosurgery; rather, it seems to be an electric treatment applied in a different way.

Dr. Juan Negrin Jr., New York: Dr. Bartle's question on the comparative results of this method and those of the usual external electric shock therapy requires an answer that I should like to know myself. We may have such an answer when a few hundred patients with adequate long follow-up studies are compared with a group of patients with similar clinical conditions treated by extrenal electric shock therapy.

Dr. Wilson asked for details on the technique, such as the milliamperage. This is not the moment to comment on these data because there are many parameters of electric current that have not yet been tried and any statement will be misleading and incomplete.

Why was extrenal electric shock therapy not used in the case presented to illustrate this method? For one reason, the patient's main clinical complaint was that of pain, which is known not to respond to electroshock therapy. Intracranial shock therapy was considered in her case when a two-stage bilateral leucotomy failed to improve her mental symptoms and her intractable pain.

I was interested to hear from Dr. Pool that other groups are carrying out similar work. From what he said, they seem to be using electric current pulses for stimulatory purposes, with the implication that they obtain therapeutic effects.

I agree with Dr. Kalinowsky that we do not know whether the type of electric current makes any difference as to the therapeutic result. The electric current we used is the standard one for electroshock therapy.

Successful Treatment for Ménière's Disease by Section of the Chorda Tympani. Dr. Samuel Rosen, New York.

The chorda tympani has always been thought to be concerned exclusively with taste. The use of the chorda tympani to cover the fenestra, as I employed it in the fenestration operation for otosclerosis, led to the experiments which proved that other functions exist for the chorda tympani. Electrical stimulation of the chorda tympani in man was found to give responses of pain, touch, tinnitus, vertigo, and facial contraction.

Section of the chorda tympani was therefore employed in cases of Ménière's diseases characterized by severe paroxysmal vertigo, deafness, tinnitus, hyperacusis, diplacusis, and episodes of

falling. The chorda tympani is sectioned by lifting up the drum membrane through the external auditory canal and exposing the nerve in the tympanum, with the use of local anesthesia. The patients is ambulatory, receives a full diet, and leaves the hospital the following day.

The results of section of the chorda tympani in 50 cases of Ménière's disease in which the symptoms had been present for 1 to 14 years were as follows: Fifty-four per cent of the patients were completely relieved of attacks of vertigo; 28% had only minor attacks, which did not keep the patient from his daily work, and 18% were not benefited. Thus, 82% of patients are free of major attacks of Ménière's disease after section of the chorda tympani.

DISCUSSION

Dr. A. M. Ornsteen, Philadelphia: Since Ménière's original description, many conflicting opinions have been expressed as to the basic physiologic mechanism of the disorder, the etiologic and precipitating factors, the classification, and the medical and surgical treatment. In review, it may be observed that autonomic dysfunction, humoral allergy, toxins, focal infections, and vitamin deficiency, all of which have been suggested as the etiologic factors in Ménière's disease, appear to act through the peripheral vascular system in a stereotyped manner, involving the arterioles, capillaries, and venules. The cause of the acute vertiginous crisis cannot be separated from the underlying causes of the disorder but must be a part of, or at least stem from, them. The evidence that Ménière's disease results from some sort of vascular disturbance seems to be overwhelming. It seems therefore that the hypothesis of localized autonomic dystonia with sudden vasospasm or vasodilatation is the most reasonable explanation for the recurring vertiginous crises.

In certain instances the hearing in the involved ear, even though improved, is not useful but is rather in the nature of a handicap. If in such a case recurring vertiginous crises appear, especially if they consist of episodes of sudden falling, surgical treatment should be considered seriously.

The "new pathway," so termed by Dr. Rosen, for Ménière's disease, namely, the chorda tympani-nervus intermedius complex, may be considered not as another basis for the syndrome, but, rather, as a new remedial approach to the problem.

Dr. Rudolph Jaeger, Philadelphia: Dr. Ornsteen's percentage of cures with his medical treatment is almost as good as Dr. Rosen's with the surgical section of the chorda tympani. One must consider what the conventional attack by the intracranial route will accomplish in Ménière's disease. In my own experience, I know of no therapy that is more specific in relieving a very distressing disease, such as Ménière's, than intracranial section of the vestibular portion of the eighth nerve. I should like to ask why, if the chorda tympani has something specific to do with Ménière's disease, one cannot get the same result, a 100% cure, with its section as one gets with the conventional method. Why does its rate of relief not compare more favorably with Dr. Ornsteen's rate of improvement, 50%, with medical treatment?

Dr. N. W. Winkelman, Philadelphia: This is the second time I have heard Dr. Rosen's paper. The first was last summer, when he read it before the Israeli Medical Association, in Jerusalem. At that time he presented two or three patients on whom he had operated some time before, with 100% relief. The results were very dramatic. It would have been more dramatic if he had illustrated this lecture with cases of cure. I believe he got 100 per cent relief in those patients whom he presented in Jerusalem. I should like to ask on how many he operated there and what results were obtained in the ones he did not mention.

Dr. Samuel Rosen, New York: I prefer not to do this simple operation until after all medical treatment has failed. I think that every patient with Ménière's disease should have the benefit of medical treatment first, and that only if it fails should the chorda tympani be sectioned. If I had Ménière"s disease on one or on both sides, preferably on one side, and I had had all available medical treatment, without benefit I certainly should prefer section of the chorda tympani (a five-minute procedure) to an intracranial section of the vestibular nerve. Section of the eighth nerve intracranially will abolish the vertigo in almost all cases of Ménière's disease, but since section of the chorda tympani seems to abolish the major attacks of vertigo in over 80% of cases, I would rather try that first; and if that fails, more drastic surgery

may be considered. A few cases in which eighth-nerve section did not relieve the vertigo have been reported in the literature. It would be intersting to try section of the chorda tympani in those cases.

As for the patients on whom I operated in Israel in 1951, three with severe Ménière's disease lost their vertigo altogether. These patients were presented a year later (1952) at the World Congress of Jewish Physicians in Jerusalem.

Spontaneous Occlusion of the Internal Carotid Artery. Dr. Emanuel Feiring, New York.

In the course of performing an estimated 500 angiograms on patients suuspected primarily of harboring intracranial tumors or vascular anomalies, seven cases of spontaneous occlusion of the internal carotid artery were encountered. On the basis of the clinical evidence alone, before angiography, a neoplasm was diagnosed in all but two cases. All the patients were men, their ages at the time they came under observation ranging from 48 to 63. The shortest duration of symptoms was two months; the longest, five years. A progressive course characterized the clinical symptoms in four cases. In the other three cases there occurred episodic manifestations, such as weakness, aphasia, and loss of consciousness, frequently transient. A hemiparesis either was evident at the time of examination or had been present at some time during the course of the illness in every instance. Electroencephalographic recordings revealed oftenest a slowing of alpha rhythm with some amplitude asymmetry, either higher or lower, and fairly diffuse delta activity, usually with focal accentuation at the frontal and temporal electrodes, all on the affected side. Pneumoencephalography disclosed symmetrically dilated ventricles and/or widened subarachnoid spaces in six cases. Improvement occurred in only two of the seven cases

DISCUSSION

Dr. N. W. Winkelman, Philadelphia: This paper is important for many reasons. First, it stresses a recently revived, and not well-known, syndrome. Second, many cases of cerebral vascular disease due to thromboses have been considered of doubtful diagnosis because of the impossibility of demonstrating conclusively the site of the occlusion. Many neuropathologists have despaired of being able to demonstrate to the clinician a thrombotic lesion in a vessel, although the history may be typical. This has given great credence to the supposition that vasospasm had played the dominant role. On the other hand, Hultquist found changes in the brain in only one-third of patients with occlusion of the anterior carotid artery below the origin of the ophthalmic branch. If "silent" occlusion does take place, one must be cautious in attributing bizarre intracranial disturbances to an occlusion as demonstrated by arteriography, for it may be only coincidental.

It is interesting that the symptom complex was described as far back as 1905 by Chiari and discussed in the American literature in 1914 by J. Ramsay Hunt, but little attention was paid to this syndrome in American literature until Egas Moniz and his angiographic method supplied us with a direct visual method of demonstrating the occlusive lesion in the internal carotid artery in the neck, even though the diagnosis could frequently be made by palpation alone.

Dr. Robert A. Groff, Philadelphia: I would like to ask Dr. Feiring whether, when performing an arteriographic study on a patient, he uses the open or the closed method. My reason in asking this question is that I had a patient admitted to the hospital with an acute occlusion syndrome of the left internal cartoid artery. My resident performed an arteriographic examination, but the internal carotid artery failed to fill. Because of certain features of the case, I had him carry out the procedure by the open method. This revealed absence of the internal carotid artery, it being represented by a thin band. Subsequently, by means of arteriograms of the right internal carotid and vertebral arteries, the altered cerebral circulation was demonstrated and both anterior cerebral arteries were found to arise from the right internal carotid artery.

Dr. Emanuel Feiring, New York: Dr. Groff's point is well taken. Both the open and the closed method of arteriography were used. I am quite sure that in each instance the common carotid artery was injected. Absence of the internal carotid artery is of such rarity that for practical purposes it can be ignored.

Anatomical Study of the Arteries of the Brain Stem. Dr. Harry A. Kaplan (by invitation) and Dr. E. Jefferson Browder, Brooklyn.

This presentation consists of a part of a study of the blood vessels of the brain which now has extended over a period of five years. During this time approximately 400 fresh brains obtained at autopsy have been injected with a radiopaque substance and stereoscopic roentgenograms made of the specimens. After a trial with the various substances and menstrua, as described by others, we have found that the combination of red lead (lead tetroxide) powder in a vinylite-acetone solution resulted in the sharpest delineation of the small vessels but that lead acetate in a vinylite-acetone solution resulted in the most constant filling of the small intrinsic vessels. The medulla, pons, and midbrain are seen to possess central perforating branches from the main arterial channel occupying the midline ventrally, similar to that in the spinal cord. Branches given off as short trunks from the basilar artery arborize almost immediately, thus entering the brain stem in a fan-like manner to supply its mesial portion. We have been unable to demonstrate any collaterals between the two sides. That portion of the medulla devoid of a ventrally placed large artery receives its central supply from caudallly directed branches of the basilar artery and rostrally directed branches of the anterior spinal artery. Even though the arrangement of the surface vessels at this level varies considerably, the intramedullary pattern conforms to standard patterns found at both higher and lower levels. The tectal and tegmental regions of the midbrain receive their blood supply from branches of the posterior cerebral artery. Seemingly, a larger number of fine branches enter these structures than enter the basilar portion. Of considerable interest was the finding that the perforating arteries in the brain stem of the younger age groups could be readily visualized by this technique, whereas fewer of these small arteries in the older age groups could be injected.

Subcortical Parietal Lobotomy for Relief of Phantom-Limb Syndrome in the Upper Extremity. Dr. J. Lawrence Pool and Dr. Thomas J. Bridges, New York.

Because spinothalamic chordotomy, resection of primary sensory cortex, other surgical procedures, and medical or psychiatric treatment may fail to relieve phantom-limb distress, particularly in an upper extremity, a different therapeutic approach was tried. This consisted of wide undercutting of the contralateral parietal cortex, an operation which we have called subcortical parietal lobotomy. Theoretically, such a procedure should interrupt thalamocortical connections of most of the sensory association cortex and therapy impair to a considerable extent the memory integration for the affected phantom part. The basis for this theory is supplied in the full text of this report.

The procedure was readily and successfully carried out over a year ago on a woman aged 65 who had an amputation of the left arm after radical mastectomy for carcinoma of the breast. Since the cranial operation she has been totally free of phantom-limb distress, which had been characterized by a sense of twisting, contorted posturing and cramp-like pressure. Some awareness of the supposed presence of the missing arm and hand returned a few weeks after operation. Intelligence and personality were not altered, and drug addiction was overcome until recently, when fresh metastases occurred. Narcotics could not be reduced abruptly, as after frontal lobotomy. The advantages of this procedure are its effectiveness, simplicity, and freedom from personality changes, seizures, and incontinence.

DISCUSSION

Dr. Robert A. Groff, Philadelphia: Dr. Francis C. Grant wishes me to express his regrets on not being able to appear to discuss this interesting paper by Dr. Pool and Dr. Bridges. As you know, and as is stated very clearly in the paper, the surgical procedures for the relief of phantom-limb pain are as yet very unsatisfactory for the upper extremity. For the lower extremity, probably the best procedure is chordotomy, which is usually successful in relieving pain. With this procedure I have had two successful results., One case is particularly interesting since the patient had amputations of the upper and lower extremities on the same side, his phantom-limb pain developing in the lower extremity alone. A high-thoracic chordotomy relieved his phantom-limb pain for over three years. He has not had pain in the upper phantom extremity.

The idea of undercutting the entire, or almost the entire, sensory cortex is an ingenious one for the treatment of this type of pain. The fact that in the case described by Dr. Pool and Dr. Bridges the memory pattern for the phantom was not abolished seems to establish the probability that the transcortical fibers are intact and play a role in the production of the memory. Because this memory pattern was not abolished, it would seem that the procedure would not be successful in all cases.

One technical comment is appropriate. Dr. Pool used needles in the cortex to delimit the anterior extension of his undercutting procedure. This method is ingenious and makes the procedure scientific.

DR. RUDOLPH JAEGER, Philadelphia: I would like to ask whether any field defects follow this section, which is so near the visual center.

DR. ALEXANDER SILVERSTEIN, Philadelphia: It is pertinent to mention at this combined meeting of the New York and the Philadelphia societies that it was a Philadelphia neurologist, S. Weir Mitchell, who made the first comprehensive contribution to this subject. He introduced the term "phantom limb," described in detail its various characteristics, and reproduced phantom-limb phenomena by electrical stimulation of the nerve stumps.

Many surgical procedures, including the simple injection of procaine into the sympathetic chain, as well as psychiatric measures, such as hypnosis and psychoanalysis, have all been reported as bringing about relief of pain in individual cases. When these procedures fail to relieve the pain, which is frequently the case, one must resort to lobotomy.

I should like to ask the authors whether they noted skin and muscle changes in their case after the extensive parietal undercutting.

DR. J. LAWRENCE POOL, New York: As to the skin-temperature changes, we did not observe any, but we did not particularly look for them. We were concentrating on reflexes, passive motion, and sensory changes.

In reply to Dr. Jaeger's question about a visual field defect: For three weeks there was a left homonymous defect, which then cleared completely. It was probably due to edema adjacent to the posterior parietal incision.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Physiology and Biochemistry

A VIRUS EFFECT ON THE UPTAKE OF C^{14} FROM GLUCOSE IN VITRO BY AMINO ACIDS IN MOUSE BRAIN. M. E. RAFELSON JR., R. J. WINZLER, AND H. E. PEARSON, J. Biol. Chem. **193**:205, 1951.

The extent of incorporation of radioactive carbon from dextrose into the amino acids of minced 1-day-old mouse brain incubated with uniformly labeled C^{14} dextrose has been studied in the presence and absence of Theiler's GD VII virus. The "proteins" were isolated, and hydrolyzed, and the component amino acids were separated by starch chromatography. Radioactive peaks of roughly comparable specific activity were found to be associated with all the nonessential and essential amino acids except proline and threonine. The presence of virus stimulated the incorporation of radioactive carbon from dextrose fragments into lysine and histidine. The amounts of these two amino acids were reduced in the virus-infected tissues, whereas the amounts of the other amino acids were unchanged. Radioactivity of lysine was shown to be limited to the carboxyl group. The carboxyl group, the methyl group, and at least one other carbon of methionine were shown to be radioactive. About half the radioactivity of phenylalanine, of leucine, and of isoleucine was shown to reside in the carboxyl carbon. The data suggest that virus propagation in this system is intimately associated with effects on lysine and histidine metabolism.

PAGE, Cleveland.

DETERMINATION OF LIPIDE INOSITOL IN ANIMAL TISSUES. W. E. TAYLOR AND J. M. MCKIBBIN. J. Biol. Chem. **201**:609, 1953.

Taylor and McKibbin have described another yeast bioassay method for the estimation of inositol. Dog's brain contained more total lipid inositol than other tissues, pancreas being the next richest tissue, but pancreas contained the greatest amount of inositol per mole of lipid phosphorus, while brain contained the least. The inositol phosphatides are minor constituents of all the tissues analyzed.

PAGE, Cleveland.

CHOLINE PHOSPHOKINASE. J. WITTENBERG AND A. KORNBERG, J. Biol. Chem. **202**:431, 1953.

An enzyme, choline phosphokinase, has been prepared from yeast which catalyzes the reaction choline + adenosinetriphosphate phosphorylcholine + adenosinediphosphate. Direct phosphorylation of choline by adenosinetriphosphate occurs in extracts of acetone powders of liver, brain, intestine, and kidney of several species.

PAGE, Cleveland.

ABSENCE OF REGENERATION IN THE SPINAL CORD OF THE YOUNG RAT. I. FEIGIN, E. H. GELLER, AND A. WOLF, J. Neuropath. & Exper. Neurol. **10**:420 (Oct.) 1951.

Regeneration of injured or severed axons of neurons whose bodies are intact does not occur to any significant extent when these processes lie within the brain or the spinal cord but occurs readily when the axons are peripheral in position. The reasons for this are obscure. As far as is known, there are no differences between the axons and myelin sheaths in the brain and spinal cord and those in the peripheral nerves. The surrounding structures vary, consisting of glial tissue in the central nervous system and Schwann cells and fibrocytes in the peripheral nervous system. It is improbable that the fibrocytes partake in favoring regeneration, but the possible function of the Schwann cells in this process has been discussed for years. The Schwann cells may affect regeneration by enzymatic influences. They may also act to provide growth pathways which guide the newly growing axons by physical means. In 1940 Sugar and Guard published data

to support this contention. They described physiologic and anatomic evidence for the successful regeneration of axons across a surgically induced gap in the spinal cord of immature rats. This was favored by the interposition of properly oriented peripheral nerve and muscle bundles.

In an attempt to confirm their observations, 102 immature rats in which the spinal cord had been transected were studied functionally and anatomically for evidence of regeneration of axons. In most of them grafts of fresh or predegenerated autogenous sciatic nerve were interposed in the spinal-cord gap. No evidence of regeneration was observed. The authors feel that previous observations suggesting regeneration may have been misinterpreted.

ALPERS, Philadelphia.

Neuropathology

VIRUS AS A PRIMARY PLASMACYTOGENIC AGENT IN BRAIN TISSUE. J. B. HYDE and B. CAMPBELL, J. Neuropath. & Exper. Neurol. **10**:408 (Oct.) 1951.

In human disease plasmacytosis has been related to hyperglobulinemia and hypersensitivity reactions. Experimental hypersensitivity in animals has been studied in this respect by many authors. These studies have revealed the intimate relation of induction of the generalized hypersensitivity to the rise in plasmacytes.

The experiments of Good consisted of microinjections of various antigenic substances, such as egg white and horse serum, into the brains of rabbits, some of which had previously been sensitized to the specific substance, others not. He found that the local "secondary response" to an antigen with which the animal had previously been sensitized was characterized by a rapid and intense accumulation of plasmacytes in the inflammatory exudate.

The present paper is an account of similar experiments in which living virus was used in place of ordinary antigens. The purpose of the experiment was to determine the time scale of the plasmacytosis, seen in the local lesions provoked by virus infection, induced in brain and skin for the purpose of comparing it with that induced by the simpler protein antigens.

Hyde and Campbell found that the early stages of inflammation brought about by the injection of minute quantities of infective vaccinia and herpes virus into the skin and brains of rabbits differ from the inflammatory picture produced by noninfective (control) material in severity of the inflammation in the amount of perivascular cuffing, and in the conspicuous early plasmacytosis. They review the significance of the plasma cell.

ALPERS, Philadelphia.

PRIMARY MASSIVE PONTINE HEMORRHAGE: A CLINICO-PATHOLOGIC STUDY. A. W. EPSTEIN, J. Neuropath. & Exper. Neurol. **10**:426 (Oct.) 1951.

Of 74 cases of primary massive intracerebral hemorrhage covered in this study, the lesion was located in the pons in 7. The clinical and pathological findings in these seven cases are described.

Primary massive pontine hemorrhage is a terminal event occurring in cases of severe hypertensive cardiovascular disease. The clinical picture is characterized by sudden onset, deep coma, bilateral neurological signs, and rapid fatal issue. The pupils are frequently miotic. Hyperpyrexia may be present in an acute destructive lesion of the pons, usually occurs terminally, and is dependent upon a suitable time interval. Convulsions, which occurred in two cases of this group, are not attributed to involvement of specific pontine areas.

The cerebrospinal fluid was grossly bloody in three of the five cases in which a lumbar puncture was performed. In another case microscopic examination revealed evidence of bleeding. The cerebrospinal fluid pressure was elevated in four of the five cases.

Complete postmortem examination was done in five of the seven cases. In all five there was cardiac hypertrophy. In two of the cases there was accelerated nephrosclerosis, and in the remaining three, microscopic evidence of renal damage. In three of the cases there was evidence of generalized arteriolosclerosis. Gross examination of the brain revealed varying degrees of atherosclerosis in six of the seven cases. The hemorrhages in the pons were bilateral in all cases. The tegmentum was never spared, but parts of the most ventral portions of the base

were spared in six cases and of the most dorsal portion in three cases. Blood was present in the ventricles in three cases and in the subarachnoid space in three cases. Microscopic examination of the brain revealed cerebral arteriolar disease in all cases.

The differential diagnosis of primary massive pontine hemorrhage is discussed. A summarized account of four cases of encephalomalacia of the pons is presented.

ALPERS, Philadelphia

Psychiatry and Psychopathology

LIFE STRESS, EMOTIONS AND PAINFUL STIFF SHOULDER. T. H. LORENZ and M. J. MUSSER. Ann. Int. Med. **37**:1232 (Dec.) 1952.

In 300 medical patients seen in consultation because they had various psychosomatic disorders the frequency of pain and stiffness of the shoulder and adjacent bodily structures was determined; the nature of these symptoms was investigated by appropriate clinical and laboratory study, and the relation between the onset and course of such complaints and the patient's emotional disturbance and reactions to life stress was evaluated.

Lorenz and Musser found that pain and stiffness in the shoulder or adjacent bodily structures occurred in 20% of these 300 patients. The onset and course of shoulder symptoms in these patients were intimately related to certain of their emotional reactions and stressful life situations.

The patients in this study who had pain and stiffness in the shoulder area were uniformly rigid, insecure, resentful, and hyperkinetic. In addition, they exhibited a characteristic pattern of dealing with stressful life situations in which they vigorously and relentlessly attacked their problems despite what seemed to them to be insurmountable difficulties. Psychologically, these persons were engaged in a continual struggle between their dependent needs and restrained resentment, on the one hand, and their aggressive drives, on the other. Physically, their excessive muscle tension seemed to act as a resistance which had to be overcome by voluntary neuromuscular effort before it could become effective. With maintenance of this reaction pattern, somatic symptoms eventually resulted.

In this series psychotherapy was added to the medical, orthopedic, and physical therapeutic measures ordinarily used in the treatment of painful stiff shoulder. The results have been encouraging. The authors suggest that the psychosomatic approach be added to other fields of specialized knowledge considered necessary for the proper evaluation and treatment of patients having pain and stiffness in the shoulder region.

ALPERS, Philadelphia

SEXUAL BEHAVIOR AFTER LOBOTOMY. J. LEVINE and H. ALBERT, J. Nerv. & Ment. Dis. **113**:332 (April) 1951.

The sexual behavior of 40 patients, from 20 to 60 years of age, who had had lobotomies six months to four years previously were studied. The sexual drive was diminished only in patients who were rendered apathetic. Generally there was a decrease in personal restraints and inhibitions, but only four patients became social problems because of this. Male patients who had had anxiety and associated impotence had satisfactory sexual activity after operation. Sexual phantasies were unaffected in content but were less vivid. The type of sexual activity was unaltered. Although the moral attitudes were unchanged, there was shallowness of the associated affect.

BERLIN, New York.

RIGHT- OR LEFT-HANDEDNESS; A PRACTICAL PROBLEM. R. S. EUSTIS, New England J. Med. **240**:249 (Feb. 17) 1949.

Eustis points out that the physician who is asked whether it is safe and wise to train an apparently left-handed child to use pencil and pen with his right hand can find good authority in the literature for almost any answer he may choose to give. Eustis believes that many apparently left-handed primary-grade children may be successfully taught to write with the right hand. When writing begins, they should all be so taught, because the use of the right

hand fits in better with the left-to-right direction of writing and also because it conforms to the custom of the majority, and hence is easier psychologically. If, however, a child objects strenuously or shows signs of nervous strain, of which stuttering may be one, the attempt should be abandoned at once, and he should be allowed to use his left hand without criticism. Those who are taught to write with the left hand should be shown the proper position of the paper, which is slanted with the top border to the right instead of to the left, as is usual. It is often necessary to drill them in the use of this position, since otherwise they are likely to imitate their right-handed neighbors. They should also be allowed to write with a slight backhand slant if they so prefer.

J. A. M. A.

Meninges and Blood Vessels

RELATIONSHIP OF EEG FINDINGS TO CLINICAL FACTORS DURING AND AFTER ACUTE PURULENT MENINGITIS. J. G. HUGHES, B. C. DAVIS, and A. E. CARPENTER, Am. J. Dis. Child. **82**:268 (Sept.) 1951.

Recent methods of treatment have resulted in dramatic reduction in mortality rates for all types of acute purulent meningitis in infancy and childhood. As more and more children survive the initial onslaught, the problem of residual disability becomes increasingly important. The authors have used electroencephalography during and after the attack of acute purulent meningitis in order to determine whether the method is useful as a prognostic tool in cases of this disease.

Electroencephalograms were obtained in 40 cases during the acute stage of purulent meningitis and at intervals thereafter, and in each instance clinical evaluation was made at the time of the electroencephalogram.

The most constant abnormalities in the electroencephalogram during the first two weeks after onset of illness were (1) marked irregularities in amplitude and rhythm in all leads, (2) a dominant, pattern of slow waves of high amplitude, and (3) in some instances, fast activity of low amplitude. Two to six weeks after onset of the disease, the chief change noted was a gradual reduction in the amount of slow activity. After six weeks there was a pronounced tendency for the electroencephalogram to return to normal. In those children who showed a slower return to a normal pattern of activity, the patterns of the initial tracing persisted, sometimes for several months, with the occasional appearance of sharp waves.

From the electroencephalographic standpoint, the eventual outcome in 19 patients followed for periods ranging from 6 to 17 months were as follows: The records were normal for 12, borderline normal for 3, and borderline abnormal for 2; none had definitely abnormal tracings. However, five of the patients whose initial electroencephalograms were the most abnormal failed to return for follow-up studies. Parents of some of these patients stated that the children were so badly damaged mentally and neurologically that they did not wish to have further studies made.

Of 26 children treated within two days of onset, only 5 were clinically abnormal when their condition was last evaluated, whereas of 12 first treated on the third day, 5 were clinically abnormal when last studied.

It was found that children who have become clinically normal after meningitis may continue to have electroencephalographic abnormalities, for variable periods, but in most cases the electroencephalogram tends to return to normal. In this study, the initial electroencephalogram was normal for 10 of 16 children with a rapid clinical response to treatment, normal for 5 of 12 who responded with moderate rapidity, and normal for only 3 of 9 whose clinical improvement was slow.

In meningitis correlation of electroencephalographic and clinical examinations is not complete. However, approximately three of four children who were clinically normal had electroencephalographic ratings within normal limits, whereas about three of four children who were clinically abnormal had electroencephalographic ratings which fell within the abnormal range. In the case of children who were clinically abnormal but had normal electroencephalograms, it is probable that damage to deeper-lying structures was not revealed in cortical brain potentials.

While the variability of clinical response in cases of acute purulent meningitis is apparent, Hughes and his colleagues believe that the electroencephalogram may detect damage to the brain which is not obvious on clinical evaluation alone and that serial electroencephalograms are of prognostic import.

ALPERS, Philadelphia.

Diseases of the Brain

EPENDYMOMA OF LATERAL VENTRICLE: REPORT OF A CASE OF MORE THAN TWELVE YEARS' SURVIVAL. A. KAPLAN, Am. J. Dis. Child. **80**:963 (Dec.) 1950.

Although gliomas in children in the cerebral hemisphere are often malignant, the ependymomas offer the best prognosis. These tumors, though infrequent, have some clinical features in common and may even be completely enucleated, with a permanent cure. Kaplan reports the present case because the patient was the youngest on record to have complete removal of an ependymoma from the lateral ventricle, because so few and such contradictory clinical findings were produced by so large a neoplasm, because ventricular studies were interesting, and because the patient survivied, in excellent health, despite the malignant histologic findings.

The patient was first seen at the age of 5 years. For 10 months he had had headache, of increasing severity and frequency. This was accompanied by matutinal vomiting. Later, yawning and nose rubbing occurred, the head gradually enlarged, vision was diminished, and for two months the gait had become increasingly unstable.

Examination showed an alert, cheerful child. The head was large, and the veins of the scalp were strikingly prominent. A definite Macewen sign was readily elicited. Vision was reduced to perception of gross finger movements. The pupils were dilated, and the fundi showed advanced papilledema with secondary optic nerve atrophy. There was horizontal nystagmus to the left. The gait was broad-based, and the extremities showed hypotonia. The finger-to-nose test was performed with slight ataxia on the right. The deep reflexes were sluggish, but there were no pathologic toe signs. The blood and urine were normal. A cerebellar neoplasm was suspected.

A trephinement of the skull was performed on the right side; 60 cc. of clear, colorless fluid was obtained from the right ventricle, and 40 cc. of air was injected. Roentgenograms of the skull showed that the right lateral ventricle was dilated but not displaced, but no air passed into the third or the left lateral ventricle. A trephinement of the skull was performed on the left side. Only 10 cc. of clear fluid was obtained, and an equal quantity of air was injected. Roentgenograms of the skull revealed a compressed left lateral ventricle with a smooth crescentic defect in the left occipital region, displacing the occipital horn downward, with some air above the displaced mass.

Operation was performed three days later, and, in spite of difficulties, a well-demarcated neoplasm was removed from the left postparietal region. The tumor weighed 191.5 gm. The pathologic diagnosis was ependymoblastoma. X-ray therapy was not given.

The patient made a good recovery and was discharged from the hospital 26 days after operation. The papilledema receded completely; the nystagmus disappeared; the dilated vessels disappeared, and the Macewen sign could no longer be elicited. Except for residual secondary optic nerve atrophy, there were no abnormal neurologic signs. Vision also improved so that faces and familiar objects could be recognized.

The boy has enjoyed excellent health in the 12 years since operation. He is attending college and finds that with the aid of his special glasses for reading he can read even the smallest print.

ALPERS, Philadelphia.

Diseases of the Spinal Cord

EXTRADURAL COMPRESSION OF THORACIC PORTION OF CORD DUE TO CHONDROMA. B. B. SPOTS, C. A. BARDECI, and J. C. CHRISTENSEN, Arq. neuro-psiquiat. **8**:77 (March) 1950.

Bruno, in 1913, was the first to describe a case in which chondroma compressed the spinal cord. Bucy, in 1930, collected 16 cases of chondroma arising from an intervertebral disk. A man aged 51 was admitted to the hospital on April 26, 1949. In October, 1948, as he ran toward

his daughter, who was in a minor accident, he felt severe pain, and had to stop suddenly because of intermittent claudication of the lower limbs, which lasted 10 minutes. He was then able to resume walking. He felt well for a few days, and then paresthesias of the lower limbs appeared. These persisted, and three months after their onset weakness of the lower limbs appeared. He was unable to walk at all for a month. Examination on admission revealed spastic paraplegia with slight movement of the left thigh; hyperreflexia of the lower limbs; a bilateral Babinski sign; marked impairment of deep sensibility in the lower limbs, more pronounced on the left than on the right, and a level for pain, touch, and temperature at the fifth thoracic dermatome, the sensory changes being greater on the right. Spinal fluid studies showed partial block, 78 mg. of total protein per 100 cc., and a negative Wassermann reaction. A roentgenogram of the spine showed a cartilaginous calcified mass at the sixth thoracic level to the left of the vertebra; there were also associated rarefaction of the body and disappearance of the left pedicle at the same level. At operation a tumor was seen pushing the dura to the right and invading the vertebral body. The tumor proved to be a chondroma.

In addition to the rarity of the tumor, the authors emphasize the unusual onset—intermittent claudication of apparently spinal cord origin. During exertion there was apparently transitory ischemia of the cord. The authors also note complete absence of pain throughout the course of the illness. In extradural tumors pain is less frequent at the onset than in intradural tumors.

N. Savitsky, New York.

Vegetative and Endocrine Systems

Simmonds' Disease (Hypopituitarism) in a Man. J. Douglas Robertson and H. F. W. Kirkpatrick, Lancet **1**:1048 (May 12) 1941.

Robertson and Kirkpatrick report the case of a man aged 44 in whom, after a sudden jerk of his neck, there developed the signs and symptoms of hypopituitarism over a four-year period. At the time of examination these signs included easy fatigability, severe attacks of headache and vomiting, polydipsia and polyuria, constipation, and impotence. Examination revealed a loss in height and weight. The fingernails were brittle and showed longitudinal striae. The body hair was scanty, and the skin was dry. The face was expressionless. There was a sinus bradycardia. The teeth were loose and carious, and the body temperature was low. The basal metabolic rate was —40%, and the cholesterol level of the blood, 130 mg. per 100 cc. There was a low 17-ketosteroid excretion. Under treatment with desoxycortisone acetate, testosterone propionate, and thyroid, the patient's condition improved considerably. In differential diagnosis anorexia nervosa, Addison's disease, myxedema, and Simmonds' disease were considered. All the evidence favored the last, the most likely cause being hemorrhage in the pituitary gland.

Madow, Philadelphia

News and Comment

ANNUAL POSTGRADUATE SEMINAR, EMBREEVILLE STATE HOSPITAL

The first annual postgraduate seminar will be held at the Embreeville State Hospital, Embreeville, Pa., on Oct. 27, 1953. Speakers will include Dr. Daniel Blain, Dr. Crawford N. Baganz, Dr. Lauren H. Smith, Dr. Arthur P. Noyes, Dr. Frederick L. Weniger, Dr. Kenneth E. Appel, and Dr. Clarence Oberndorf.

Address all communications to the superintendent, Dr. Jess V. Cohn, Embreeville State Hospital, Embreeville, Pa.

AMERICAN ACADEMY FOR CEREBRAL PALSY

The seventh annual meeting of the American Academy for Cerebral Palsy will be held on Oct. 30 and 31, 1953, in Fort Worth, Texas, at the Western Hills Hotel.

The scientific sessions are open to members of the medical or allied professions. Guests will be required to pay a registration fee.

Correspondence may be addressed to Dr. Harry E. Barrett, secretary, 116 S. Michigan Ave., Chicago.

MASSACHUSETTS DEPARTMENT ON MENTAL HEALTH

Nineteenth Postgraduate Seminar in Neurology and Psychiarty

A review course in basic neurology and psychiatry, is offered under the auspices of the Metropolitan State Hospital and the Psychiatric Training Faculty of Massachusetts, Inc.

Thirty lectures, given every Monday, from 2 to 8:30 p. m., from Oct. 5 to Dec. 7, 1953, will be given at the Metropolitan State Hospital, 475 Trapelo Rd., Waltham Mass.

Course in Child Psychiatry, Walter E. Fernald State School

A course in child psychiatry (pediatric neuropsychiatry) is offered at the Walter E. Fernald State School, Waverley, Mass., from Oct. 7 to Dec. 2, 1953. Eight Seminars will be held, covering various aspects of dynamic and developmental neuropsychiatry, including the problems of childhood schizophrenia, mental deficiencies, emotional reactions, and cerebral palsies. Each seminar will be held in a two-hour session on Wednesday, from 7 to 9 p. m., during October and November and on December 2, with one speaker as chairman and other speakers as invited guests to a round table discussion. The individual sessions will be announced later.

All interested should apply before Oct. 1, 1953, to Dr. Malcolm J. Farrell, Walter E. Fernald State School, Waverley, Mass.

FIRST INTERNATIONAL CONGRESS ON GROUP PSYCHOTHERAPY

The International Committee of Group Psychotherapy invites all persons and groups who are interested in group psychotherapy to participate in the Congress. The memberships of the sponsoring committees include representatives of all varieties of group psychotherapy, without discrimination. Among the sponsoring organizations are the American Society of Group Psychotherapy and Psychodrama and the American Sociometric Association. The aim is to have a real, all-embracing Congress in order that it may serve the development and integration of the entire field. Communications should be addressed to the director, organizing committee, J. L. Moreno, M.D., Room 327, 101 Park Ave., New York 17, for further information.

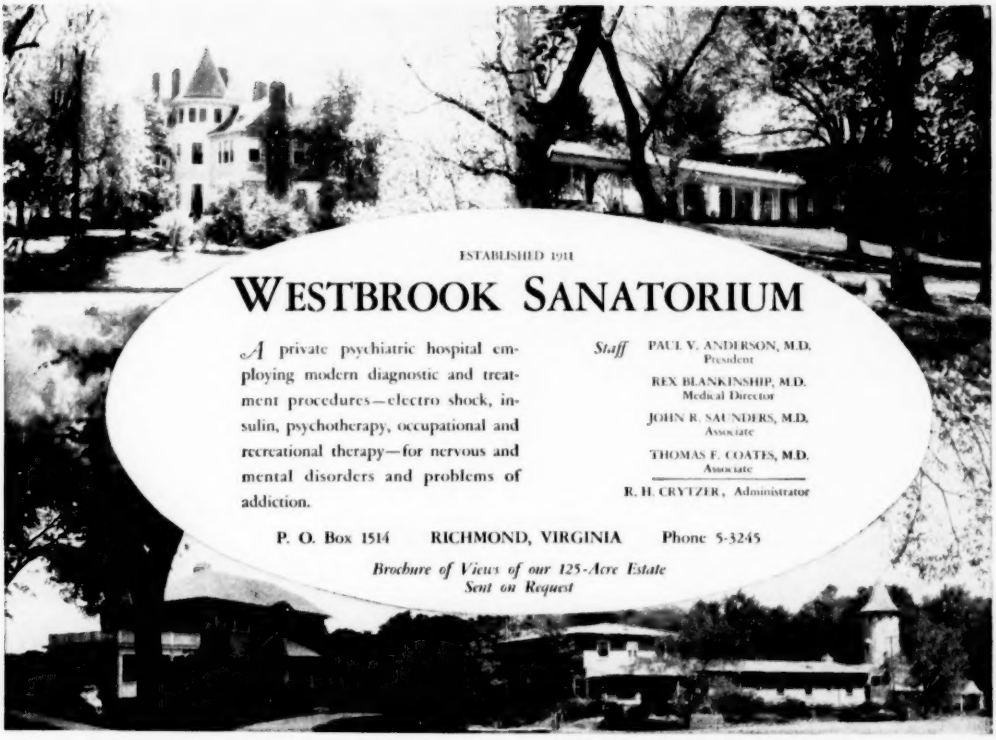
FELLOWSHIPS, JEWISH SANITARIUM AND HOSPITAL FOR CHRONIC DISEASES

The establishment of two fellowships for clinical and experimental research has been announced by the trustees of the Jewish Sanitarium and Hospital for Chronic Diseases. The fellowships, named in honor of the president of the hospital, Mr. Isaac Albert, will be awarded during the fall of 1953.

Applicants should write to the hospital superintendent, Arthur Feigenbaum, Rutland Rd. and E. 49th St., Brooklyn.

MEETING OF AMERICAN ACADEMY OF FORENSIC SCIENCES

The American Academy of Forensic Sciences will hold its sixth annual meeting, Feb. 25, 26, and 27, 1954, at the Drake Hotel, Chicago. Titles of all papers to be read must be submitted to Dr. Milton Helpern, program chairman, 106 E. 85th St., New York 28, by Nov. 1, 1953.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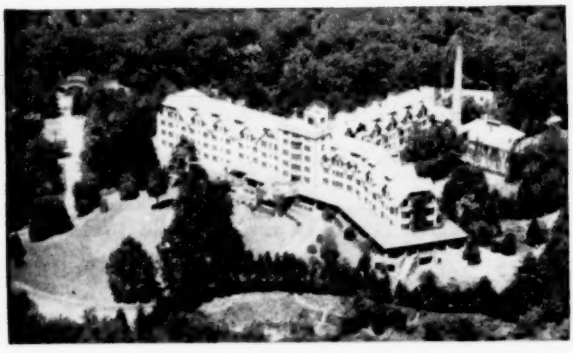

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